Controlled Substances Act Scheduling Process

Lynn Whipkey Mehler, J.D.
Senior Counsel
FDA Office of the Chief Counsel

Controlled Substances Act (CSA)

- First enacted in 1970 to regulate the manufacture, importation, possession, use, and distribution of certain substances.
- While DEA is primarily responsible for interpreting and enforcing the CSA, the Department of Health and Human Services (HHS) has a number of responsibilities, several of which are performed by FDA.

Drug Scheduling Process

- FDA completes a medical and scientific assessment and scheduling recommendation for HHS with the concurrence of the National Institute on Drug Abuse (NIDA).
- The HHS scheduling recommendation is binding on DEA as to scientific and medical matters and DEA cannot schedule a substance if HHS recommends that it not be controlled.
- DEA schedules substances through rulemaking.
- DEA requested HHS perform a scientific assessment and scheduling recommendation for dextromethorphan.

CSA Schedules

- 5 Schedules under the CSA
- Schedule I is the most restrictive and substances in schedule I are not available for medical use.
- FDA approved drugs are controlled in schedules II through V.
- A substance's schedule dictates the requirements regarding physical security, quotas, prescription and registration requirements.
- Section 202 of the CSA establishes the 5 schedules. DEA regulations at 21 CFR Part 1308 list the substances that are controlled in each schedule.

CSA Eight Factors

Section 201(c) of the CSA requires the following factors be considered in the HHS scheduling evaluation:

1. Actual or relative potential for abuse
2. Scientific evidence of it's pharmacological effect, if known
3. The state of current scientific knowledge regarding the substance
4. It's history and current pattern of abuse
5. The scope duration, and significance of abuse
6. What, if any, risk there is to the public health
7. The substance's psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled.

Scheduling Recommendation

- After considering the eight factors, HHS must make a recommendation as to the appropriate schedule.
- Each schedule has three findings that must be made.
- The findings for each schedule are set out in section 202 of the CSA.

Schedule Findings

- **Schedule I**
  High potential for abuse
  No currently accepted medical use in treatment in the U.S.
  Lack of accepted safety for use under medical supervision

- **Schedule II**
  High potential for abuse
  Currently accepted medical use in treatment in the U.S. or a currently accepted medical use with severe restrictions
  Abuse of the substance may lead to severe psychological or physical dependence

- **Schedule III**
  Potential for abuse less than substances in schedules I or II
  Currently accepted medical use in treatment in the U.S.
  Abuse of the substance may lead to moderate or low physical dependence or high psychological dependence

Schedule Findings Cont.

- **Schedule IV**

  Low potential for abuse relative to substances in schedule III

  Currently accepted medical use in treatment in the U.S.

  Abuse of the substance may lead to limited physical dependence or psychological dependence relative to substances in schedule III

- **Schedule V**

  Low potential for abuse relative to substances in schedule IV

  Currently accepted medical use in treatment in the U.S.

  Abuse of the substance may lead to limited physical dependence or psychological dependence relative to the substances in schedule IV

Unscheduled Status of Dextromethorphan

- Dextromethorphan is not currently controlled under the CSA.
- When the CSA was enacted, section 201(g)(2) specifically excluded dextromethorphan from being a controlled substance.
- However, the CSA provided that dextromethorphan could be added to the CSA through the traditional scheduling process, if warranted.

CSA Exclusion of Non-Narcotic OTC Drugs from Scheduling

Section 201(g)(1) of the CSA provides the following:

> The Attorney General shall by regulation exclude any non-narcotic drug that contains a controlled substance from the schedules if such drug may, under the Federal Food, Drug, and Cosmetic Act, be lawfully sold over the counter without a prescription.

Definition of “Narcotic Drug” in the CSA

Section 102(17) of the CSA defines “narcotic drug” as “any of the following, whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:

(A) Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers.

(B) Poppy straw and concentrate of poppy straw.

CSA Definition of Narcotic Drug cont.

(C) Coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed.

(D) Cocaine, its salts, optical and geometric isomers, and salts of isomers.

(E) Ecgonine, its derivatives, their salts, isomers, and salts of isomers.

(F) Any compound, mixture, or preparation which contains any quantity of any of the substances referred to in subparagraphs (A) through (E).”

CSA Exclusion of Non-Narcotic, lawfully marketed OTC Drugs

- Dextromethorphan does not meet the definition of a “narcotic drug” under the CSA.
- Dextromethorphan is available in FDA approved prescription products as well as lawfully marketed non-prescription (OTC) drugs.
- DEA regulations set out a process for applying for exclusion from the schedules for any drug product that meets the criteria in 201(g)(1) of the CSA.

Summary

- Before dextromethorphan can be scheduled, FDA must complete a medical and scientific analysis and scheduling recommendation and DEA will have to go through rulemaking.
- If the substance dextromethorphan is scheduled, sponsors of lawfully marketed OTC products containing dextromethorphan will be able to apply to DEA for an exemption.
- If DEA grants the exemption, the OTC drug product will not be scheduled.
- Dextromethorphan in bulk, FDA approved prescription products, or drug products not lawfully marketed will not be eligible for the exemption from scheduling and will be required to comply with the requirements of the CSA and DEA regulations for the relevant schedule.

Regulatory History and Background on Over-the-Counter Dextromethorphan

Drug Safety and Risk Management Advisory Committee
September 14, 2010

Ayana K. Rowley, Pharm.D
Interdisciplinary Scientist
Division of Nonprescription Regulation Development
Office of Drug Evaluation IV

Overview

- OTC Drug Review
- Regulatory History of Dextromethorphan
- 1990 and 1992 Advisory Committee Meetings on Dextromethorphan Abuse

Pharmacy Retail Shelf

Monograph or NDA?

Regulation of OTC Drugs

- New Drug Application (NDA)
  - Pre-marketing approval
  - Drug Product Specific
  - Confidential (Filing and Review)
  - Marketing Exclusivity

- OTC Drug Review (Monograph)
  - No pre-marketing approval
  - Active Ingredient Specific
  - Public Process - Notice and Comment Rulemaking
  - No Marketing Exclusivity

OTC Drug Review

- 1962 Drug Amendments Act
  - More than 300,000 OTC drug products
  - 500 considered safe under an NDA
    - Of these 25% found to be effective
- Initiated on May 11, 1972
  - Classified into over 80 different therapeutic categories
    - Included up to 800 active ingredients
      - *Acne* to *weight control* drug products

OTC Monographs

Advisory Review Panel

- **Category I: GRASE (Generally Recognized as Safe and Effective)**
- **Category II: not GRASE**
- **Category III: cannot determine if Safe and Effective**

OTC Monographs

Federal Register / Vol. 68, No. 110 / Monday, June 9, 2003 / Rules and Regulations 34273

comment on the direct final rule. FDA stated that the effective date of the direct final rule would be December 8, 2003, and, if the agency received no significant adverse comments, it would publish a notice of confirmation of the effective date no later than June 11, 2003. FDA received no significant adverse comments within the comment period. Therefore, FDA is confirming that the effective date of the direct final rule is December 8, 2003. As noted in the direct final rule, FDA is publishing this confirmation document 180 days before the effective date to permit affected firms adequate time to take appropriate steps to bring their bottled water products into compliance with the quality standard imposed by the new rule.

Dated: June 2, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–14477 Filed 6–6–03; 8:45 am]

BILLING CODE 4164–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 350, and 3

[Docket No. 78N–0064]

RIN 0910–AA01

Antiperspirant Drug Products Fo Over-the-Counter Human Use; Fin Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, issued as a tentative final monograph (TFM), and all new data and information on antiperspirant drug products that have come to the agency's attention.

DATES: *Effective Date:* This rule is effective December 9, 2004.

Compliance Dates: The compliance date for products with annual sales less than $25,000 is June 9, 2005. The compliance date for all other products is December 9, 2004.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

In the **Federal Register** of October 10, [43 FR 46694], FDA published an advance notice of proposed rulemaking to establish a monograph for OTC antiperspirant drug products, together with the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products (the Panel), which evaluated the data on these products. The agency's proposed regulation (TFM) for OTC antiperspirant drug products was published in the **Federal Register** of August 20, 1982 (47 FR 36492).

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective and are misbranded. These ingredients included seven antiperspirant ingredients, which are included in § 310.545(a)(4) (21 CFR 310.545(a)(4)). In this rulemaking, the agency is adding one additional ingredient to this section. (See section III.1 of this document.)

In the **Federal Register** of March 23, 1993 (58 FR 15452), the agency requested public comment on two citizen petitions, and a response to one of the petitions, related to the safety of aluminum compounds in OTC antiperspirant drug products. This final monograph completes the TFM and provides the substantive response to the citizen petitions.

Twenty-four months after the date of publication in the **Federal Register**, for products with annual sales less than $25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final monograph that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

In response to the TFM on OTC antiperspirant drug products and the request for comment on the citizen petitions, the agency received 20 comments. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs on six different issues. Copies of the information considered by the Panel, the comments, and the hearing request are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. "OTC Volumes" cited in this document refer to information on public display.

The agency received some "feedback" communications under the OTC drug review procedures (see the **Federal Registers** of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)). The agency has included these communications in the administrative record and addressed them in this document.

The safety issues raised by the citizen petitions are discussed in section II.F of this document. The agency believes it has adequately responded to the six issues related to the hearing request; therefore, a hearing is not necessary.

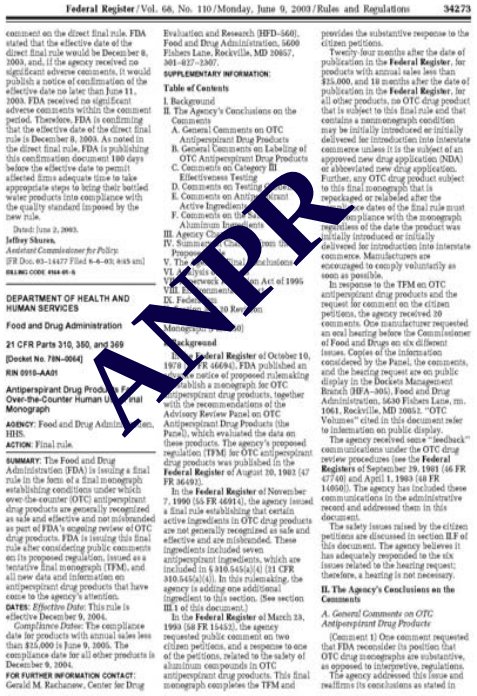
II. The Agency's Conclusions on the Comments

A. General Comments on OTC Antiperspirant Drug Products

(Comment 1) One comment requested that FDA reconsider its position that OTC drug monographs are substantive, as opposed to interpretive, regulations.

The agency addressed this issue and reaffirms its conclusions as stated in

OTC Monographs



Federal Register / Vol. 68, No. 110 / Monday, June 9, 2003 / Rules and Regulations 34273

comment on the direct final rule. FDA stated that the effective date of the direct final rule would be December 8, 2003, and, if the agency received no significant adverse comments, it would publish a notice of confirmation of the effective date no later than June 11, 2003. FDA received no significant adverse comments within the comment period. Therefore, FDA is confirming that the effective date of the direct final rule is December 8, 2003. As noted in the direct final rule, FDA is publishing this confirmation document 180 days before the effective date to permit affected firms adequate time to take appropriate steps to bring their bottled water products into compliance with the quality standard imposed by the new rule.

Dated: June 2, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–14477 Filed 6–6–03; 8:45 am]

BILLING CODE 4164–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 350, and 369

[Docket No. 78N–0064]

RIN 0910–AA01

Antiperspirant Drug Products For Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, issued as a tentative final monograph (TFM), and all new data and information on antiperspirant drug products that have come to the agency's attention.

DATES: *Effective Date:* This rule is effective December 9, 2004.

Compliance Dates: The compliance date for products with annual sales less than $25,000 is June 9, 2005. The compliance date for all other products is December 9, 2004.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

In the **Federal Register** of October 10, 1978 (43 FR 46694), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC antiperspirant drug products, together with the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products (the Panel), which evaluated the data on these products. The agency's proposed regulation (TFM) for OTC antiperspirant drug products was published in the **Federal Register** of August 20, 1982 (47 FR 36492).

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective and are misbranded. These ingredients included seven antiperspirant ingredients, which are included in § 310.545(a)(4) (21 CFR 310.545(a)(4)). In this rulemaking, the agency is adding one additional ingredient to this section. (See section III.1 of this document.)

In the **Federal Register** of March 23, 1993 (58 FR 15452), the agency requested public comment on two citizen petitions, and a response to one of the petitions, related to the safety of aluminum compounds in OTC antiperspirant drug products. This final monograph completes the TFM and provides the substantive response to the citizen petitions.

Twenty-four months after the date of publication in the **Federal Register**, for products with annual sales less than $25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final monograph that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

In response to the TFM on OTC antiperspirant drug products and the request for comment on the citizen petitions, the agency received 20 comments. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs on six different issues. Copies of the information considered by the Panel, the comments, and the hearing request are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. "OTC Volumes" cited in this document refer to information on public display.

The agency received some "feedback" communications under the OTC drug review procedures (see the **Federal Register** of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)). The agency has included these communications in the administrative record and addressed them in this document.

The safety issues raised by the citizen petitions are discussed in section II.F of this document. The agency believes it has adequately responded to the six issues related to the hearing request; therefore, a hearing is not necessary.

II. The Agency's Conclusions on the Comments

A. General Comments on OTC Antiperspirant Drug Products

(Comment 1) One comment requested that FDA reconsider its position that OTC drug monographs are substantive, as opposed to interpretive, regulations.

The agency addressed this issue and reaffirms its conclusions as stated in

ANPR

TFM

OTC Monographs

Federal Register / Vol. 68, No. 110 / Monday, June 9, 2003 / Rules and Regulations 34273

comment on the direct final rule. FDA stated that the effective date of the direct final rule would be December 8, 2003, and, if the agency received no significant adverse comments, it would publish a notice of confirmation of the effective date no later than June 11, 2003. FDA received no significant adverse comments within the comment period. Therefore, FDA is confirming that the effective date of the direct final rule is December 8, 2003. As noted in the direct final rule, FDA is publishing this confirmation document 180 days before the effective date to permit affected firms adequate time to take appropriate steps to bring their bottled water products into compliance with the quality standard imposed by the new rule.

Dated: June 2, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–14477 Filed 6–6–03; 8:45 am]

BILLING CODE 4164–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 350, and

[Docket No. 78N–0064]

RIN 0910–AA01

Antiperspirant Drug Products For Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, issued as a tentative final monograph (TFM), and all new data and information on antiperspirant drug products that have come to the agency's attention.

DATES: *Effective Date:* This rule is effective December 9, 2004.

Compliance Dates: The compliance date for products with annual sales less than $25,000 is June 9, 2005. The compliance date for all other products is December 9, 2004.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

In the **Federal Register** of October 10, 1978 (43 FR 46694), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC antiperspirant drug products, together with the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products (the Panel), which evaluated the data on these products. The agency's proposed regulation (TFM) for OTC antiperspirant drug products was published in the **Federal Register** of August 20, 1982 (47 FR 36492).

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective and are misbranded. These ingredients included seven antiperspirant ingredients, which are included in § 310.545(a)(4) (21 CFR 310.545(a)(4)). In this rulemaking, the agency is adding one additional ingredient to this section. (See section III.1 of this document.)

In the **Federal Register** of March 23, 1993 (58 FR 15452), the agency requested public comment on two citizen petitions, and a response to one of the petitions, related to the safety of aluminum compounds in OTC antiperspirant drug products. This final monograph completes the TFM and provides the substantive response to the citizen petitions.

Twenty-four months after the date of publication in the **Federal Register**, for products with annual sales less than $25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final monograph that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

In response to the TFM on OTC antiperspirant drug products and the request for comment on the citizen petitions, the agency received 20 comments. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs on six different issues. Copies of the information considered by the Panel, the comments, and the hearing request are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. "OTC Volumes" cited in this document refer to information on public display.

The agency received some "feedback" communications under the OTC drug review procedures (see the **Federal Registers** of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)). The agency has included these communications in the administrative record and addressed them in this document.

The safety issues raised by the citizen petitions are discussed in section II.F of this document. The agency believes it has adequately responded to the six issues related to the hearing request; therefore, a hearing is not necessary.

II. The Agency's Conclusions on the Comments

A. General Comments on OTC Antiperspirant Drug Products

(Comment 1) One comment requested that FDA reconsider its position that OTC drug monographs are substantive, as opposed to interpretive, regulations.

The agency addressed this issue and reaffirms its conclusions as stated in

TFM

Federal Register / Vol. 68, No. 110 / Monday, June 9, 2003 / Rules and Regulations 34273

comment on the direct final rule. FDA stated that the effective date of the direct final rule would be December 8, 2003, and, if the agency received no significant adverse comments, it would publish a notice of confirmation of the effective date no later than June 11, 2003. FDA received no significant adverse comments within the comment period. Therefore, FDA is confirming that the effective date of the direct final rule is December 8, 2003. As noted in the direct final rule, FDA is publishing this confirmation document 180 days before the effective date to permit affected firms adequate time to take appropriate steps to bring their bottled water products into compliance with the quality standard imposed by the new rule.

Dated: June 2, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–14477 Filed 6–6–03; 8:45 am]

BILLING CODE 4164–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 350, and 369

[Docket No. 78N–0064]

RIN 0910–AA01

Antiperspirant Drug Products For Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antiperspirant drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, issued as a tentative final monograph (TFM), and all new data and information on antiperspirant drug products that have come to the agency's attention.

DATES: *Effective Date:* This rule is effective December 9, 2004.

Compliance Dates: The compliance date for products with annual sales less than $25,000 is June 9, 2005. The compliance date for all other products is December 9, 2004.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background
II. The Agency's Conclusions on the Comments
A. General Comments on OTC Antiperspirant Drug Products
B. General Comments on Labeling of OTC Antiperspirant Drug Products
C. Comments on Category III Effectiveness Testing
D. Comments on Testing Guidelines
E. Comments on Antiperspirant Active Ingredients
F. Comments on the Safety of Aluminum Ingredients
III. Agency Conclusions
IV. Summary of Changes From the Proposed Rule
V. The Agency's Findings and Conclusions
VI. Economic Impact
VII. Paperwork Reduction Act of 1995
VIII. Federalism Impact
IX. Section 301 of the 1990 Revision
X. References
Monograph (Part 350)

I. Background

In the **Federal Register** of October 10, 1978 (43 FR 46694), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC antiperspirant drug products, together with the recommendations of the Advisory Review Panel on OTC Antiperspirant Drug Products (the Panel), which evaluated the data on these products. The agency's proposed regulation (TFM) for OTC antiperspirant drug products was published in the **Federal Register** of August 20, 1982 (47 FR 36492).

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective and are misbranded. These ingredients included seven antiperspirant ingredients, which are included in § 310.545(a)(4) (21 CFR 310.545(a)(4)). In this rulemaking, the agency is adding one additional ingredient to this section. (See section III.1 of this document.)

In the **Federal Register** of March 23, 1993 (58 FR 15452), the agency requested public comment on two citizen petitions, and a response to one of the petitions, related to the safety of aluminum compounds in OTC antiperspirant drug products. This final monograph completes the TFM and provides the substantive response to the citizen petitions.

Twenty-four months after the date of publication in the **Federal Register**, for products with annual sales less than $25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final monograph that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

In response to the TFM on OTC antiperspirant drug products and the request for comment on the citizen petitions, the agency received 20 comments. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs on six different issues. Copies of the information considered by the Panel, the comments, and the hearing request are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. "OTC Volumes" cited in this document refer to information on public display.

The agency received some "feedback" communications under the OTC drug review procedures (see the **Federal Registers** of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)). The agency has included these communications in the administrative record and addressed them in this document.

The safety issues raised by the citizen petitions are discussed in section II.F of this document. The agency believes it has adequately responded to the six issues related to the hearing request; therefore, a hearing is not necessary.

II. The Agency's Conclusions on the Comments

A. General Comments on OTC Antiperspirant Drug Products

(Comment 1) One comment requested that FDA reconsider its position that OTC drug monographs are substantive, as opposed to interpretive, regulations.

The agency addressed this issue and reaffirms its conclusions as stated in

FM

What is in a Monograph?

- Active ingredient (GRASE)
  - Dosage forms
  - Dose or concentration
  - Permitted combinations
- Drug Facts Label
  - Use (indication)
  - Warnings
  - Directions

- OTC Drug Review
- Regulatory History of Dextromethorphan
- 1990 and 1992 Advisory Committee Meetings on Dextromethorphan Abuse

Regulatory History of Dextromethorphan

- 1976- Advance Notice of Proposed Rulemaking
  - Cough, Cold, Allergy, Bronchodilator and Antiasthmatic ANPR for OTC Human Use (41 FR 38312)

- Dextromethorphan and Dextromethorphan Hydrobromide
  - “Non-narcotic antitussive agent”
  - “No significant abuse liability”
  - Category I (GRAS/E)

Regulatory History of Dextromethorphan (cont'd)

- 1983 Antitussive Drug Products TFM (48 FR 48576)
  - Proposed labeled directions and warnings
  - "…dextromethorphan has a wide margin of safety with respect to its potential to cause poisoning through accidental overdose…"
  - "…no fatalities have been reported even with doses in excess of 100 times the normal adult dose..."
  - "…low order of toxicity, dextromethorphan is probably the safest antitussive presently available..."

Regulatory History of Dextromethorphan (cont'd)

- 1987 Antitussive Drug Products FM (52 FR 30042)
- Indicated Populations
  - Adults and Children over 2 years of age
    - Cough suppressant
  - Maximum Daily Dose
    - Adults and children 12 years and over: not to exceed 120 mg (in 24 hours)
    - Children 6 to under 12 years of age: not to exceed 60 mg
    - Children 2 to under 6 years of age: not to exceed 30 mg

- OTC Drug Review
- Regulatory History of Dextromethorphan
- 1990 and 1992 Drug Abuse Advisory Committee Meetings on Dextromethorphan Abuse

1990 Advisory Committee Overview

- Citizen Petitions from Pennsylvania and Utah
- Reports of abuse with dextromethorphan-containing cough syrups by teenagers
  - Slang terms for
    - Dextromethorphan: DM, Robo, Rojo, and Velet
    - Dextromethorphan Intoxication: Robo Tripping, Skittling and Dexing

1990 Advisory Committee Objectives

- Help FDA identify and better define the extent of the problem
- Develop a strategy for assessing the problem
- Identify and discuss the pros and cons of possible solutions that can be applied

1990 Advisory Committee Conclusions

- The sponsor should provide additional
  - Toxicity data in higher dose ranges
  - National epidemiological data

- Agreement to follow up during the next six months or when appropriate

1992 Advisory Committee Summary

- Follow Up to 1990 AC meeting
- No clear consensus of the extent of the problem or what actions should be taken to control it
  - Conduct future studies that focus attention on the areas where the outbreaks are occurring
  - Collect clinical behavioral and pharmacology data using higher doses of dextromethorphan

Regulatory History of Over-the-Counter Dextromethorphan containing Drug Products

Drug Safety and Risk Management Advisory Committee
September 14, 2010

Ayana K. Rowley, Pharm.D.
Interdisciplinary Scientist
Division of Nonprescription Regulation Development
Office of Drug Evaluation IV

Abuse-Related Pharmacology of Dextromethorphan

Katherine Bonson, Ph.D.
Pharmacologist
Controlled Substance Staff
CDER - FDA

Overview of Presentation

- Chemistry
- Receptor Binding
- Preclinical Behavioral Studies
- Human Pharmacokinetics
- Human Experience and Clinical Studies
- Human Deaths and Overdoses
- Human Adverse Events

Information Utilized

- We have not received primary data from any assessments of the abuse potential of DXM, either preclinically or clinically.
- Thus, this presentation relies on publicly-available information found in the scientific and medical literature.
- This information includes data from well-conducted studies, as well as from anecdotal case reports.

Chemistry of Dextromethorphan

- DXM is the methylated dextrorotatory analog of the synthetic Schedule II opioid, levorphanol, a derivative of codeine (Bem and Peck, 1992).

- Levorphanol can also be converted to the Schedule II opioids, racemethorphan and levomethorphan, the racemic and levorotatory forms of DXM (Braenden and Wolfe, 1954).

Controlled Substances Act: DXM as a Non-Narcotic Drug

- Under Controlled Substance Act (CSA) definition, DXM is not a “narcotic drug” and is not currently scheduled under the CSA.
- Thus, DXM is different from the Schedule II “narcotic” compounds to which it is structurally-related, such as levorphanol, levomethorphan and racemethorphan.

Receptor Binding Studies

Receptor Binding Studies: Mu-Opioid Receptors

- Even though DXM is derived from opiate drugs, it has no significant affinity for mu-opioid receptors (Chen et al., 1991).
- Dextrorotatory drugs typically do not have high affinity for the mu-opioid receptor, unlike levorotatory drugs (Snyder, 1977).

Receptor Binding Studies: Mu-Opioid Receptors

- Although DXM has no affinity for mu opioid sites, opiates that are structurally similar to DXM -- such as levorphanol, levomethorphan and racemethorphan -- have high affinity at the mu opioid site.

Receptor Binding Studies: Five Mechanisms for DXM

Receptor binding studies show that DXM has 5 known pharmacological mechanisms of action:

- NMDA receptor channel blocker
- sigma-1 receptor agonist
- calcium channel blocker
- serotonin reuptake inhibitor
- nicotinergic antagonist

Receptor Binding Studies: NMDA Receptor (PCP Site)

- DXM binds with moderate affinity (Ki = 510 nM) at the “PCP site” of the NMDA receptor-channel complex (Murray and Leid, 1984).
- DXM acts as a noncompetitive antagonist at the PCP-NMDA site (Franklin and Murray, 1992). This is thought to be the primary mechanism of action of DXM.

Receptor Binding Studies: Sigma-1 Sites

- At sigma-1 receptor sites, DXM acts as a high-affinity agonist (Ki = 50-142 nM) (Zhou and Musacchio, 1991; Maurice et al., 2001).

Receptor Binding Studies: Calcium Channel Sites

- DXM induces inhibition of voltage-dependent calcium channels, creating a functional antagonism (Netzer et al., 1993; Carpenter et al., 1988).

Receptor Binding Studies: Serotonin Transporter

- DXM has high affinity binding for the serotonin transporter (Meoni et al., 1997), producing serotonin reuptake inhibitory activity (Gillman, 2005).

Receptor Binding Studies: Nicotine Sites

- DXM acts as an antagonist at nicotinergic acetylcholine receptors (Damaj et al., 2005).

Preclinical Behavioral Studies with Dextromethorphan

General Behavioral Effects of DXM in Animals

- DXM (60-100 mg/kg, i.p.) produces stereotypy in rats that is similar to that produced by the NMDA antagonists, PCP (Schedule II) and ketamine (Schedule III) (Ishmael et al., 1998).

- DXM (15-120 mg/kg, i.p.) also produces hyperactivity in rats that is similar to that produced by PCP (Schedule II) (Szekely et al., 1991).

Self-Administration Studies with DXM in Animals

- Self-administration is a method that tests whether a drug has rewarding properties in animals. Animals are trained to press a lever a certain number of times to receive an intravenous dose of a known drug of abuse.

- A test drug is then substituted and if that drug has rewarding properties, it will maintain lever-pressing in the animals.

Self-Administration Studies with DXM in Animals

In animals trained to self-administer the NMDA antagonist, PCP (Schedule II):

- DXM maintains self-administration in monkeys at moderate doses (100-300 µg/kg/infusion) (Nicholson et al.,1999)
- DXM does not maintain self-administration at lower (30 µg/kg/infusion) or higher doses (1000 µg/kg/infusion) in monkeys and rats (Nicholson et al., 1999).

Self-Administration of NMDA Antagonists in Animals

Self-administration is also produced by other NMDA antagonists, including:

- PCP (Schedule II) (Winger et al., 2002)
- Ketamine (Schedule III) (Broadbear et al., 2004).

Drug Discrimination with DXM in Animals

- In drug discrimination, animals are trained to differentially press one of two levers after administration of a training drug or placebo.
- If a test drug produces similar “interoceptive cues” to the training drug, more than 80% of the animal’s response will be on the training drug-associated lever.
- In this case, the test drug is said to “generalize” to the training drug.

Drug Discrimination with DXM in Animals: NMDA (PCP) Site

In animals trained to discriminate the NMDA antagonist, PCP (Schedule II), from saline:

- Rats dose-dependently generalize DXM to the PCP cue (Nicholson et al., 1999).
- Monkeys (2 of 3) generalize DXM to the PCP cue, with the third monkey showing partial generalization (Nicholson et al., 1999).

Drug Discrimination with DXM in Animals: NMDA (PCP) Site

When another NMDA antagonist, ketamine (Schedule III), was used as the training drug in a discrimination study:

- DXM dose-dependently produced full generalization to the ketamine cue in rats (Narita et al., 2001).
- PCP (Schedule II) also produced full generalization to the ketamine cue in rats (Narita et al., 2001).

Drug Discrimination with DXM in Animals: Sigma-1 Site

- When monkeys were trained to discriminate the sigma-1 agonist, (+)pentazocine (Schedule IV), from saline, DXM produced full generalization to the (+)pentazocine cue (White and Holtzman, 1982).

Human Pharmacokinetics of Dextromethorphan

Pharmacokinetics of DXM

- In humans, DXM is well absorbed after oral ingestion, with a Tmax of ~1.7 to 2.5 hours (Meyyanathan et al., 2008).
- Onset of effect is rapid, often beginning ~15 to 30 minutes after oral ingestion (Pender & Parks, 1991).
- The half-life of DXM is ~2.5 hours (Meyyanathan et al., 2008)

Human Metabolism of DXM

- DXM converts through O-demethylation to its major metabolite, dextrorphan (DXO). This is catalyzed by the cytochrome P-450 isozyme 2D6 (CYP2D6) following oral administration (Schmider et al., 1997).
- DXO, like its parent compound, DXM, has high affinity for the NMDA channel site (Murray et al., 1984).

Abuse-Related Human Experience and Clinical Studies with DXM

DXM Dose Response

- The recommended therapeutic dose of DXM for the treatment of cough is 10-30 mg (p.o.), every 4-8 hours.
- Abuse of DXM occurs at doses ranging from ~100 mg to >2000 mg (p.o.).
- Clinical abuse-related studies with DXM use doses ranging from 10 mg to 315 mg (p.o.) and 10 mg to 240 mg (s.c.).

DXM Effects in Humans

There are four plateaux of subjective responses to DXM (Boyer, 2004, review paper):

- First plateau (1.5 to 2.5 mg/kg; 105-175 mg/70 kg): mild intoxication and gastrointestinal symptoms
- Second plateau (2.5 to 7.5 mg/kg; 175-525 mg/ 70 kg): lethargy, agitation, ataxia and tachycardia
- Third plateau (7.5 to 15 mg/kg; 525-1050 mg/70 kg): frank psychotic symptoms, disorientation, altered judgment
- Fourth plateau (> 15 to 30 mg/kg; 1050-2100 mg/ 70 kg): full dissociative states, hyperthermia, with risk of seizures and aspiration

Clinical Study Overview

- There are five human abuse potential studies conducted with DXM since 1953.
- Three of these studies evaluated whether DXM produced opioid-like effects in non-tolerant, non-dependent opioid abusers.
- One study evaluated the alcohol-like effects in detoxified alcoholics and healthy subjects.
- One study evaluated the abuse-related subjective effects of DXM in healthy subjects.

Clinical Studies with DXM

Isbell and Fraser, 1953:

- Administration of DXM (10 to 100 mg, p.o. and s.c.) to non-tolerant, former morphine abusers did not produce morphine-like subjective responses. However, levorphanol, levomethorphan and racemethorphan did produce morphine-like effects.
- DXM (60 to 75 mg, p.o. and s.c.) produced adverse events such as dizziness, headache, double vision, nausea and vomiting.

Clinical Studies with DXM

Jasinski et al., 1971:

- Administration of DXM to opioid abusers (120, 240 mg, p.o.; 60, 120 and 240 mg, s.c.) did not produce increases on subjective scales for “Drug Liking” or “Euphoria”.
- DXM produced increases on subjective scales for “Sedation” and “Dysphoria”.
- DXM was identified as a barbiturate (Schedules II to IV) but not as an opioid.

Clinical Studies with DXM

Jasinski et al., 2000:

- Administration of DXM (180 mg, p.o.) to "opiate abusers" did not increase ratings on "Feel Drug", "Euphoria" or "Drug Liking".
- However, this dose of DXM did increase ratings on "Dislike Drug".

Clinical Studies with DXM

Soyka et al., 2000:

- Administration of DXM (140 mg, p.o.) to detoxified alcoholics and to healthy volunteers increased ratings on the Alcohol Sensations Scale.
- Alcoholic subjects also had an increase in “Craving for Alcohol” following DXM administration.

Clinical Studies with DXM

Zawertailo et al., 2010:

Administration of DXM (140, 210, 315 mg, p.o.) to healthy volunteers increased ratings on:

- Positive subjective scales (“Euphoria”, “High”, “Drug Liking”, “Good Effects”).
- Negative subjective scales (“Dysphoria”, “Sedation”, “Bad Effect”, “Unpleasantness”, Dizziness”).

Human Effects of Dextrorphan

- Two studies evaluated whether the DXM metabolite, DXO, is responsible for the psychoactive effects of DXM (Zawertailo et al., 1998 and 2010), using either poor and extensive CYP2D6 metabolizers, or quinidine to inhibit CYP2D6 activity.
- These small studies (n = 6-8) suggest that both DXM and DXO contribute positive and negative subjective responses to the overall experience following DXM ingestion.

Human Deaths and Overdoses with DXM Reported in the Medical Literature

Deaths from DXM

- In 2005, five teenage males in Washington state, Florida and Virginia died following ingestion of DXM, with or without other drugs.
- In each case, the deaths were deemed to be the result of direct toxic effects of DXM (Logan et al., 2009).
- These five deaths led to the publication of an FDA Talk Paper on DXM ("*FDA Warns Against Abuse of Dextromethorphan*", May 20, 2005) to warn the public about the risks associated with abuse of DXM.

Deaths from DXM

Case Reports from Bellingham, WA:

- Two young men (17 and 19 years old) ingested DXM and were found dead at home.
- An autopsy found pulmonary edema, cerebral edema and frothy foam in major airways.
- The cause of death was determined to be acute DXM intoxication in both cases.
- Both individuals tested positive for cannabinoids and one tested positive for diphenhydramine.

Deaths from DXM

Case Reports from Bellingham, WA (con't):

- A bag with 47 gm of white powder was found with a label that said, "Dextromethorphan Hbr 100 g, not for human use."
- The young men had obtained the DXM from "Chemical API," a chemical resale company in Indianapolis that purchased powdered DXM from India, repackaged the substance and resold it over the Internet.
- The young men repackaged the DXM into gelatin capsules, which they intended to sell.

Deaths from DXM

Case Report from Danville, Virginia:

- A 19 year old young man ingested DXM and was found unresponsive and later pronounced dead.
- The only finding upon autopsy was pulmonary edema. The cause of death was deemed to be DXM toxicity.
- The young man had also obtained the DXM from “Chemical API.”

Deaths from DXM

Case Reports from Cape Coral, Florida:

- Two 19 year old young men ingested powdered DXM (from “Chemical API”), Robitussin HL (containing DXM) and OTC Benadryl (diphenhydramine) and were later found dead.
- Autopsy reports showed that both individuals had heavy, wet, congested lungs. The cause of death was deemed to be DXM toxicity.

DXM Overdoses Associated with the Case Reports of Death

- In the Washington case report, at least three non-fatal overdoses were linked to the sale of capsules containing powdered DXM by one of the young men who died.
- In the Florida case report, one male youth ingested the same amounts of DXM and diphenhydramine. He survived the drug ingestion because he became ill and vomited -- and because he weighed 70 pounds more than his friends who died.

Summary of Case Reports of DXM Deaths and Overdoses

- In these published case reports, all 5 deaths and all 4 overdoses associated with DXM involved the ingestion of illicit, powdered, non-pharmaceutical DXM -- with or without the presence of other drugs (including pharmaceutical DXM).

Adverse Events Associated with DXM

CNS-Related Adverse Events with DXM

- The medical and scientific literature has reported on adverse events (AEs) resulting from acute ingestion of DXM for over 50 years.
- These CNS-related AEs include: mood changes, perceptual alterations, inattention, disorientation and aggressive behavior, nausea, restlessness, insomnia, ataxia, slurred speech, nystagmus (Hildebrand et al., 1989, among other citations).

Non-CNS-Related Adverse Events with DXM

- In a review of medical case reports published through 2008, doses of DXM greater than 2 mg/kg (~140 mg) produce tachycardia, hypertension, respiratory depression (Ramanelli and Smith, 2008) .
- Severe folate deficiencies have also been reported in DXM abusers (Au et al., 2007).

Adverse Events Resulting from DXM-HBr

- DXM is typically found as a hydrobromide salt, so bromism is possible in chronic users.
- Bromism symptoms include memory impairment, drowsiness, tremors and ataxia, skin eruptions, and psychiatric symptoms (delirium or psychosis) (Ng et al., 1992).
- However, bromism is rare and requires very high serum bromide levels (Horowitz, 1997).

Summary of Preclinical and Clinical Data with DXM

Summary of DXM Preclinical Pharmacology

- DXM is primarily an NMDA antagonist with no affinity for mu-opioid receptors.
- Like other scheduled NMDA antagonists, DXM is self-administered by animals.
- In drug discrimination, DXM generalizes to scheduled NMDA antagonists and sigma-1 agonists.

Summary of DXM Clinical Pharmacology

- DXM abuse at supratherapeutic doses produces 4 plateaux of subjective effects, with increasing degrees of intoxication.
- In clinical studies, DXM does not produce opioid-like effects, but does produce abuse-related subjective responses.
- Five deaths and four overdoses are associated with illicit DXM.
- Both CNS and non-CNS AEs are reported with DXM abuse.

Role of Dextromethorphan in Treatment of Cough: A Clinical Perspective

Priscilla Callahan-Lyon, M.D.
Division of Nonprescription Clinical Evaluation
ODE IV, CDER

Presentation Outline

- Brief History
- Dextromethorphan as a monograph ingredient
  - Approved Indications
  - Review of references used to support monograph inclusion
- Current Clinical Perspectives
  - American College of Chest Physician (ACCP) Guidelines
  - Review of references used to support clinical guidelines
- Conclusions

Sources of Information

- FDA Cough and Cold Proposed Rule, Tentative Final Monograph, and Final Rule
  - Reference articles reviewed by FDA Panel
- ACCP Evidence-Based Clinical Guidelines
  - Published literature references; primary data not reviewed by FDA
- Other Professional Organization Clinical Guidelines (AHRQ National Guidance Clearinghouse, American College of Physicians, American Lung Association, American College of Family Medicine)
  - Refer to ACCP guidance

Dextromethorphan

- One of three compounds tested in research seeking “nonaddictive substitutes for codeine”
- Available as OTC cough suppressant since 1958
- Included in original ‘Cough and Cold’ monograph Proposed Rule in 1976 (41FR38312)

Allowed OTC Cough Ingredients

Final Rule – August 1987 (52 FR 30042)

Antitussive Active Ingredients:

1. Oral (taken by mouth, acts systemically)
   a. Chlophendianol HCl
   b. Codeine, Codeine phosphate, Codeine sulfate
   c. Dextromethorphan, Dextromethorphan HBr
   d. Diphenhydramine citrate, Diphenhydramine HCl
2. Topical (relieves cough when inhaled or after application to throat or chest or when dissolved as a lozenge)
   a. Camphor
   b. Menthol

Availability of OTC Cough Ingredients

Ingredient	**OTC Availability**
Chlophendianol	Not Marketed in U.S.
Codeine	Not Available OTC (Behind the counter in some states)
Dextromethorphan	Widely Available OTC
Diphenhydramine	Not Marketed as cough med
Camphor	Widely Available
Menthol	Widely Available

Dextromethorphan – Final Rule

Approved Indications

1. Temporarily relieves cough due to minor bronchial irritation as may occur with a cold

2. Temporarily relieves cough associated with the common cold

Dextromethorphan – Final Rule
Approved Indications

Additional statements allowed by monograph

a) Temporarily decreases impulse to cough
b) Temporarily helps you cough less
c) Temporarily helps suppress cough reflex
d) Temporarily reduces intensity of cough
e) Reduces the cough impulse to help you sleep
f) Calms the cough center and relieves cough
g) Non-narcotic cough suppressant for the temporary control of cough

Monograph References (Reviewed by FDA Panel)

- Benson, et al, 1953; tested 6 drugs (including DXM) in dogs
- Stefko, et al, 1961; tested 9 antitussive drugs (including DXM) on cats and dogs
  - Both studies showed cough suppression efficacy of DXM comparable to codeine
  - Both studies showed DXM less sedating than codeine

Monograph References (Reviewed by FDA Panel)

Bickerman, et al, 1957; evaluated response to treatments in 15 healthy humans after citric acid vapor exposure to induce cough

- DXM dose of 10 mg reduced number of coughs by 26.3% over four hours
- Codeine dose of 30 mg reduced number by 22.4% over four hours
- Placebo had no activity

Monograph References (Reviewed by FDA Panel)

Cass, et al, 1954; treated 120 hospitalized human subjects with persistent cough

- Compared three doses of DXM with codeine and placebo
- Dose-response demonstrated for DXM
- All doses of DXM and codeine beat placebo
- DXM and codeine had equal antitussive effect (mg for mg) but codeine has more ‘ill effects’

Monograph References (Reviewed by FDA Panel)

Ralph, 1954; studied DXM in 183 patients - symptomatic and asymptomatic (many with TB); no comparator

- Moderate to marked improvement in cough (as judged by an observer) in 84% of symptomatic subjects
- 20 subjects received 75 mg daily for 32 days with no significant ill effects

Current Clinical Perspective

Clinical Evaluation of Cough

- One of most common symptoms for which patients seek medical attention
- Per 2003 CDC statistics
  - Acute URI most common illness-related diagnosis at ED visits
  - Leading patient complaints for ED visits were abdominal pain, chest pain, fever, and cough

Clinical Evaluation of Cough

Evaluation focuses on etiology and duration of cough

- Cough defined as acute, sub-acute, or chronic
- Cough has multiple possible etiologies and patients may have more than one reason to cough
- Duration is a consideration for clinicians
  - OTC labeling addresses duration for length of treatment but not for treatment initiation

Clinical Guidelines

- Systematically developed statements designed to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances
- Produced under auspices of medical specialty associations (private or governmental) – i.e., not individuals
- Corroborating documentation available
- Guidelines are not a FDA document

American College of Chest Physicians (ACCP)

- Leading professional organization focusing on respiratory diseases
- Originally published evidence-based consensus panel report on cough in 1998; updated in 2006
- Panel had extensive worldwide representation
- Recommendations graded by panel based on quality of evidence (looking at study design and strength of methodologies)
- References are published literature – primary data not FDA reviewed

ACCP 2006
Cough Treatment Guidelines

Recommendations based on scale:

- A – Strong
- B – Moderate
- C – Weak
- D – Negative
- I – Inconclusive (no recommendation possible)
- E – Expert Opinion Only (limited clinical data)

ACCP 2006 Cough Treatment Guidelines

Chronic Cough due to Acute Bronchitis:

In patients with a diagnosis of acute bronchitis, antitussive agents are occasionally useful and can be offered for short-term symptomatic relief of coughing.

Grade of Recommendation: C (weak)

Antitussive agents = dextromethorphan and codeine

ACCP 2006 Cough Treatment Guidelines

Chronic Cough due to Chronic Bronchitis:

In patients with chronic bronchitis, central cough suppressants such as codeine and dextromethorphan are recommended for short-term symptomatic relief of coughing.

Grade of Recommendation: B (moderate)

ACCP 2006
Cough Treatment Guidelines

Post Infectious Cough not due to bacterial sinusitis or early pertussis infection

Central acting antitussive agents such as codeine and dextromethorphan should be considered when other measures fail.

Grade of Recommendation: E/B (moderate; expert opinion)

Other measures = inhaled ipratropium, inhaled steroids, or oral steroids

ACCP 2006 Cough Treatment Guidelines

Cough due to URI

In patients with cough due to URI, central cough suppressants (codeine, dextromethorphan) have limited efficacy for symptomatic relief and are not recommended.

Grade of Recommendation: D (negative)

ACCP 2006 Cough Treatment Guidelines

Acute Cough due to the Common Cold (subset of URI)

In patients with acute cough due to the common cold, over-the-counter combination cold medications (including dextromethorphan), with the exception of an older antihistamine-decongestant, are not recommended until randomized controlled trials prove they are effective cough suppressants.

Grade of Recommendation: D (negative)

ACCP 2006 Cough Treatment Guidelines References

Parvez, et al, 1996; single dose, PC, DB, RCT of 451 patients with cough due to acute URI

- Study done at pharmaceutical research center
- Study completed over 3 cold “seasons”
- “Cough counts” decreased with DXM compared to placebo; 19 – 36% depending on year
- Only statistically different at certain time points during dosing interval, not for entire treatment period

ACCP 2006 Cough Treatment Guidelines References

Lee, et al, 2000; 43 patients, single dose, DB, stratified, randomized and parallel group evaluation of DXM and placebo for cough associated with URI

- Measured cough sound pressure, cough frequency, and subjective severity score
- Both DXM and placebo had decreases in all areas but difference between groups not statistically significant

ACCP 2006 Cough Treatment Guidelines References

Pavesi, et al, 2001; Meta-analysis with

pooled data comparing DXM with placebo

- 6 studies (710 patients) randomized, DB, PC, single-dose; adults with URI
- All sponsored by pharmaceutical company
- DXM demonstrated statistically significant difference for total cough bouts, effort, and latency (average 12-17% for all parameters)
- Individual studies not powered to show statistically significant differences

Additional Reference

Smith, et al, 2009; Cochrane Review of OTC medications for acute cough in children and adults in ambulatory settings

- 25 trials (17 in adults); 3492 participants (2876 adults)
- DXM included in 3 trials (Lee, Parvez, Pavesi)
- Author's conclusion: "There is no good evidence for or against the effectiveness of OTC medicines in acute cough. Many studies were of low quality and very different from each other, making evaluation of overall efficacy difficult."

Conclusions

- Cough is a common symptom for which patients seek treatment
- Studies using dextromethorphan show a modest effect on cough
- The options for OTC cough therapy are very limited; practically speaking dextromethorphan is the only available systemically active OTC cough medicine

Over-the-Counter and Outpatient Utilization Trends for Dextromethorphan

Tracy Pham, Pharm.D
Drug Utilization Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology
September 14, 2010

Outline

- National OTC sales data for dextromethorphan (DM) products, Years 2005 - 2009
  - Dosage form
  - Active ingredients
- Outpatient prescription (Rx) data for dextromethorphan products and cough/cold products, Years 2000 – 2009
  - Active ingredients
  - Patient age
  - Prescribing specialties
- Limitations
- Summary

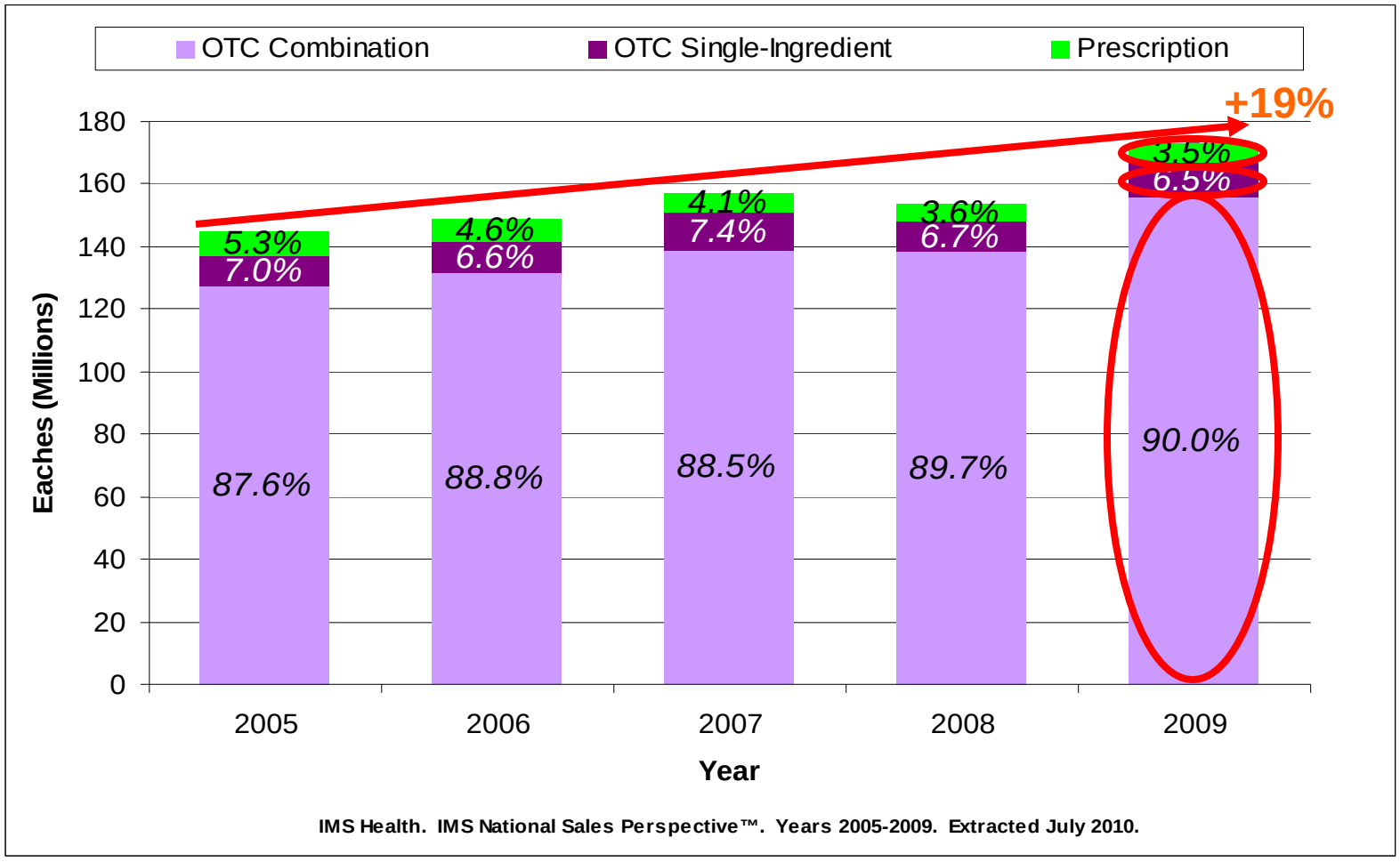
Over-the-Counter Sales Data
Years 2005-2009

IMS Health, IMS National Sales Perspective™

Database Description
IMS Health, IMS National Sales Perspective™

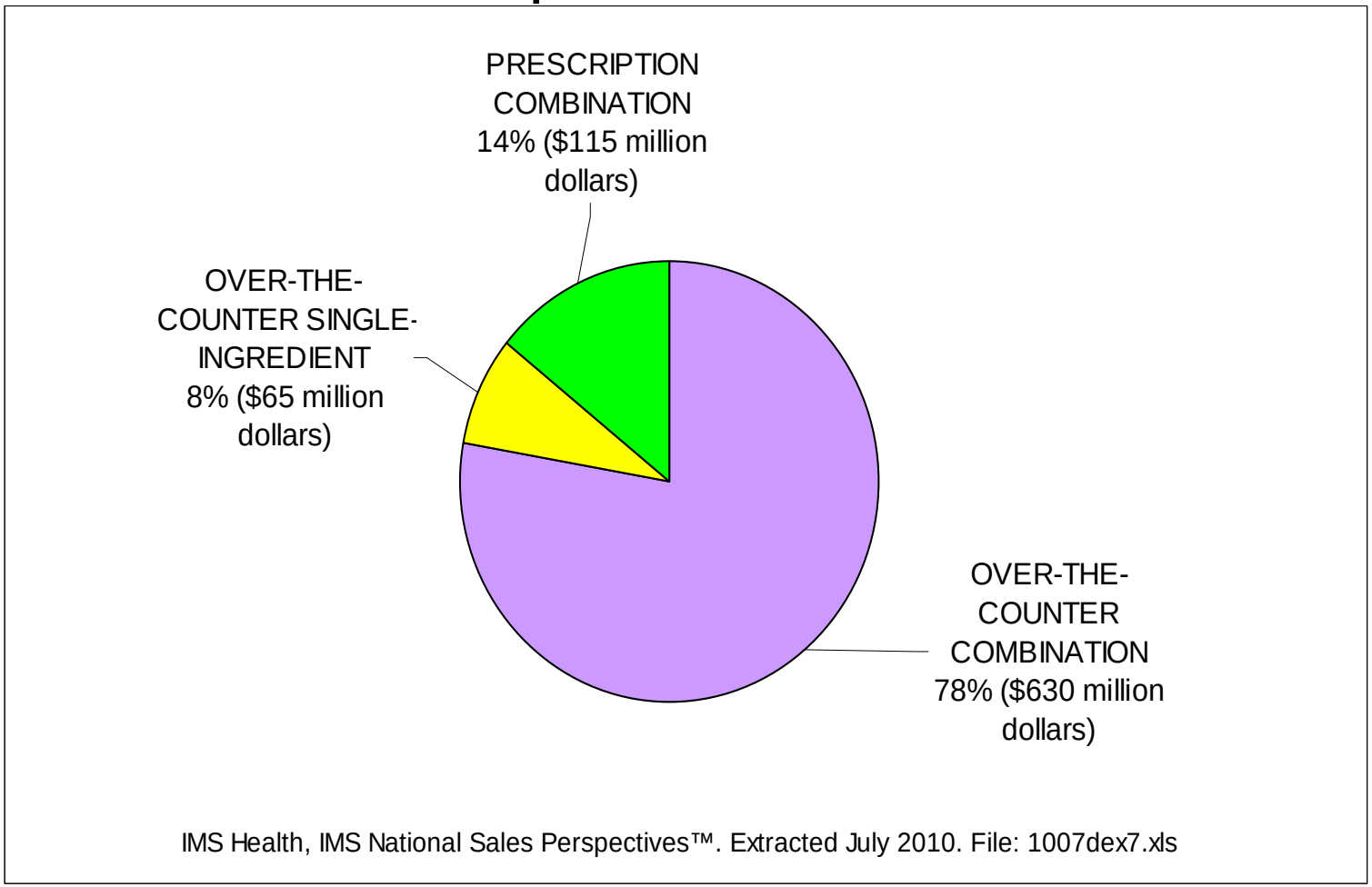
- Measures the volume of prescription (Rx) and OTC drug products sold from manufacturers to retail and non-retail channels of distribution
- **Eaches (EA)** are the number of packets, bottles, and vials of a product shipped in a unit
- Retail settings include: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service
- Non-retail settings include: clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

Total Sales and Market Share Percentage of Over-the-Counter and Prescription Dextromethorphan Products, Years 2005-2009



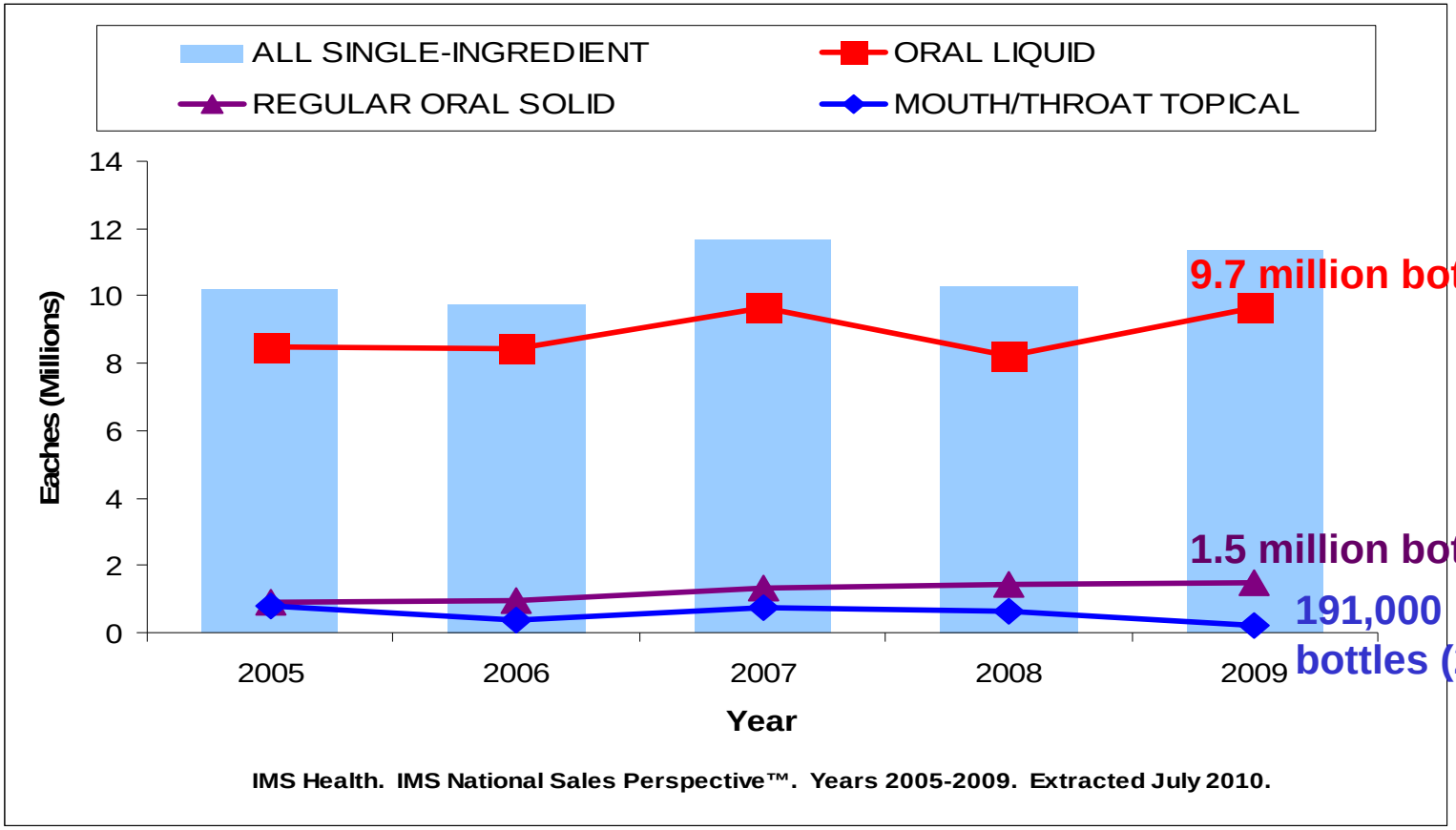
IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010.

Market Share Percentage of the Total Dollar Amounts of Dextromethorphan Products, Year 2009



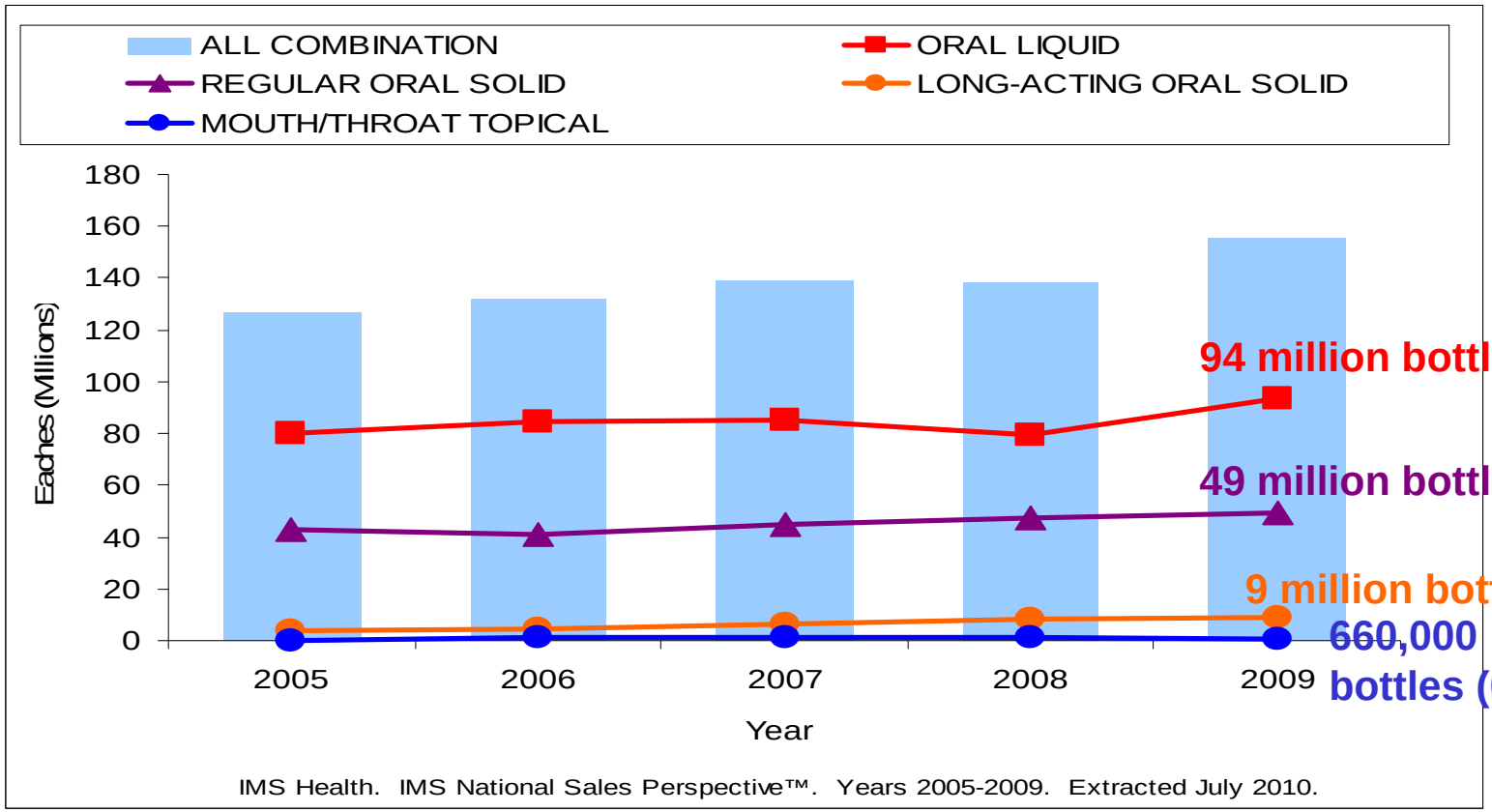
IMS Health, IMS National Sales Perspectives™. Extracted July 2010. File: 1007dex7.xls

Sales of Over-the-Counter Single-Ingredient Dextromethorphan Products by Dosage Form, Years 2005-2009



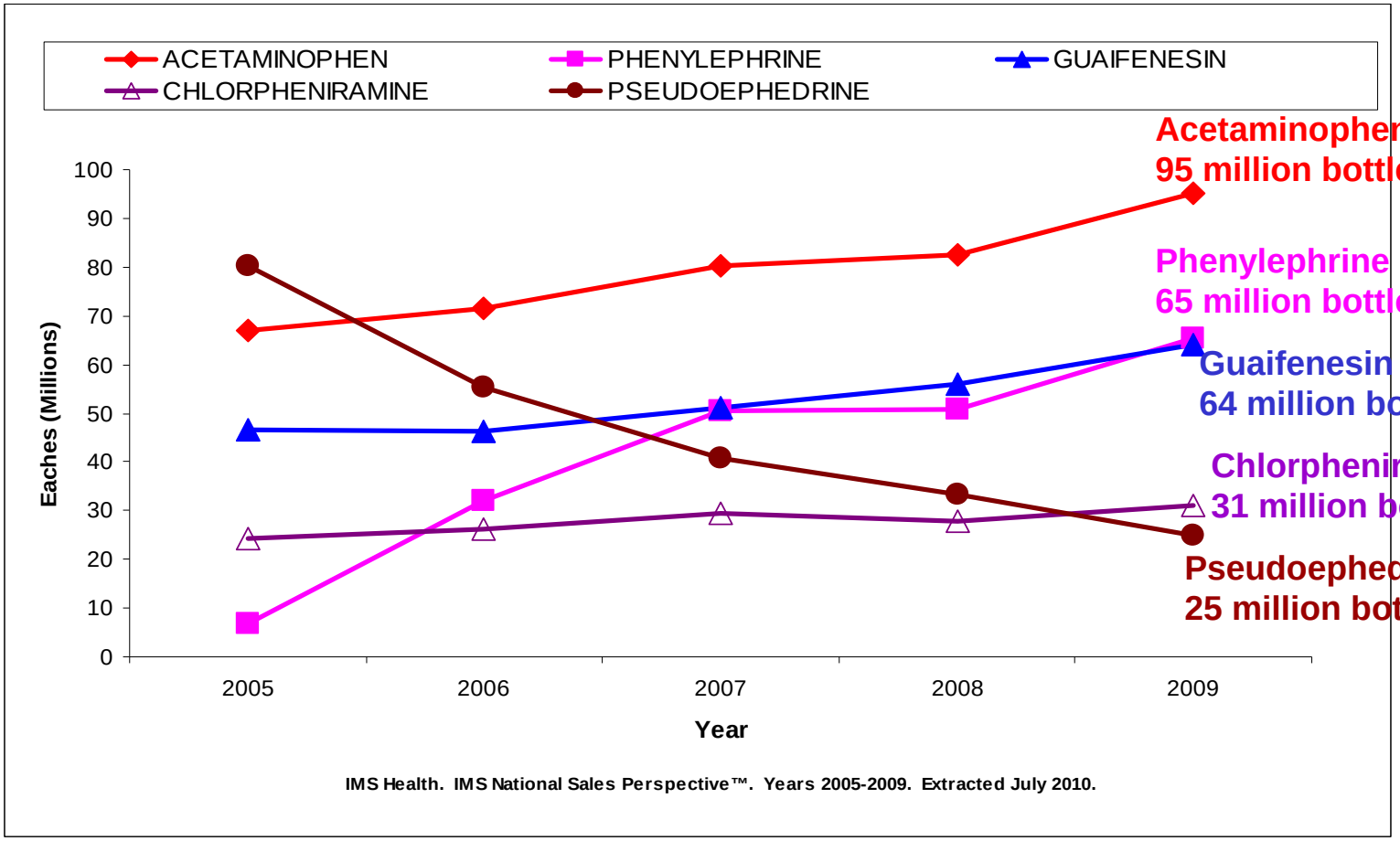
- No reported sale of concentrated oral drops formulation in y2009

Sales of Over-the-Counter Combination Dextromethorphan Products by Dosage Form, Years 2005-2009



- Concentrated oral drops formulations accounted for 0.5% of oral liquid formulations sale market in y2009.

Sales of Over-the-Counter Combination Dextromethorphan Products by Top 5 Co-Active Ingredients, Years 2005-2009



IMS Health. IMS National Sales Perspective™. Years 2005-2009. Extracted July 2010.

Prescription-Level Data for Dextromethorphan Containing Products

Years 2000-2009

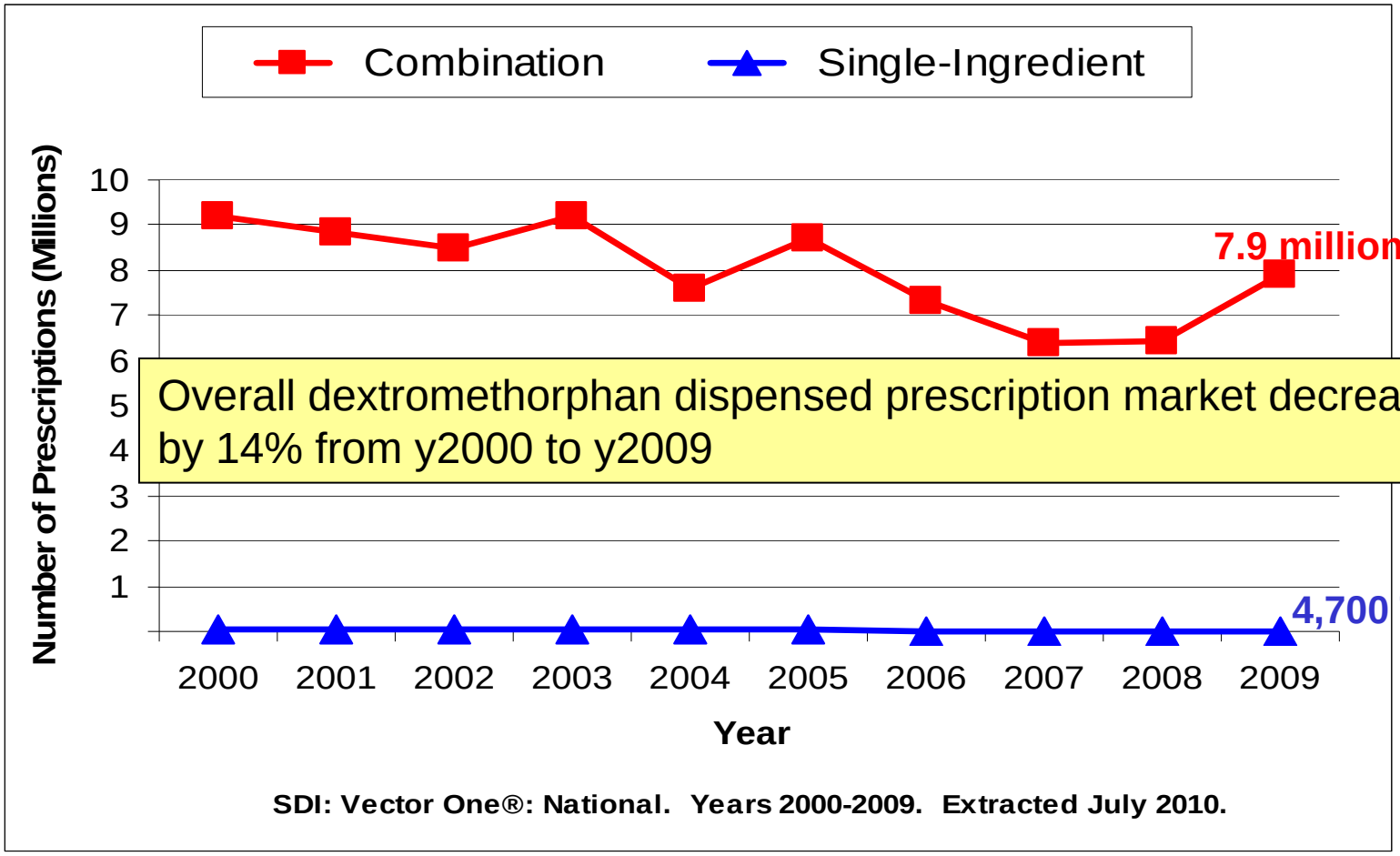
SDI, Vector One®: National (VONA)

Database Description
SDI, Vector One®: National (VONA)

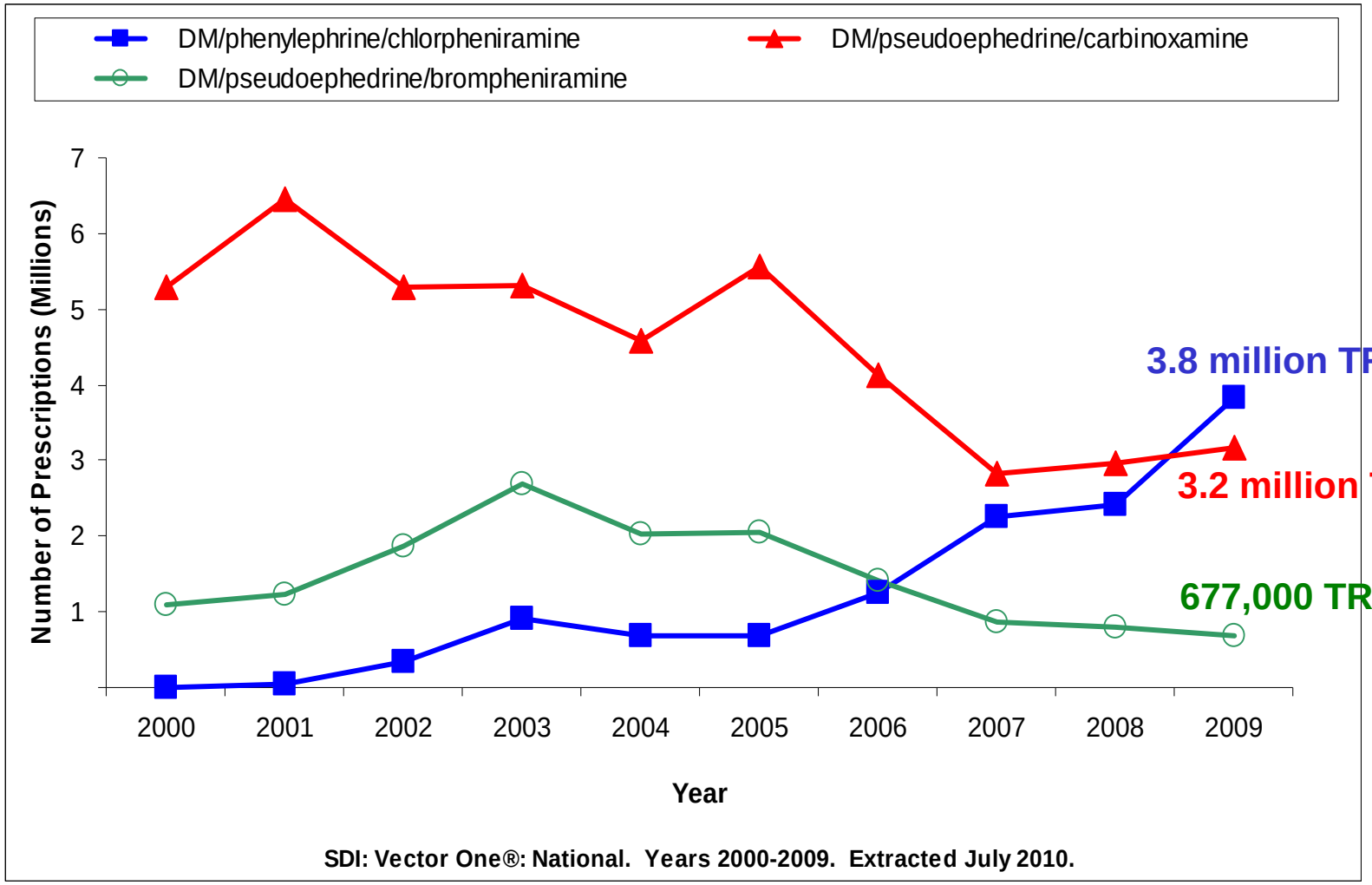
- National-level projected prescription and patient-centric tracking service
  - Over 2.0 billion prescription claims per year
  - Over 160 million unique patients
  - Approximately 59,000 U.S. retail pharmacies

- Retail pharmacies include:
  - National retail chains
  - Mass merchandisers
  - Pharmacy benefits managers and their data systems
  - Provider groups

Projected Number of Outpatient Dispensed Prescriptions for Dextromethorphan Products, Years 2000-2009



Projected Number of Outpatient Dispensed Prescriptions for Combination Dextromethorphan Products by Active Ingredients, Years 2000-2009



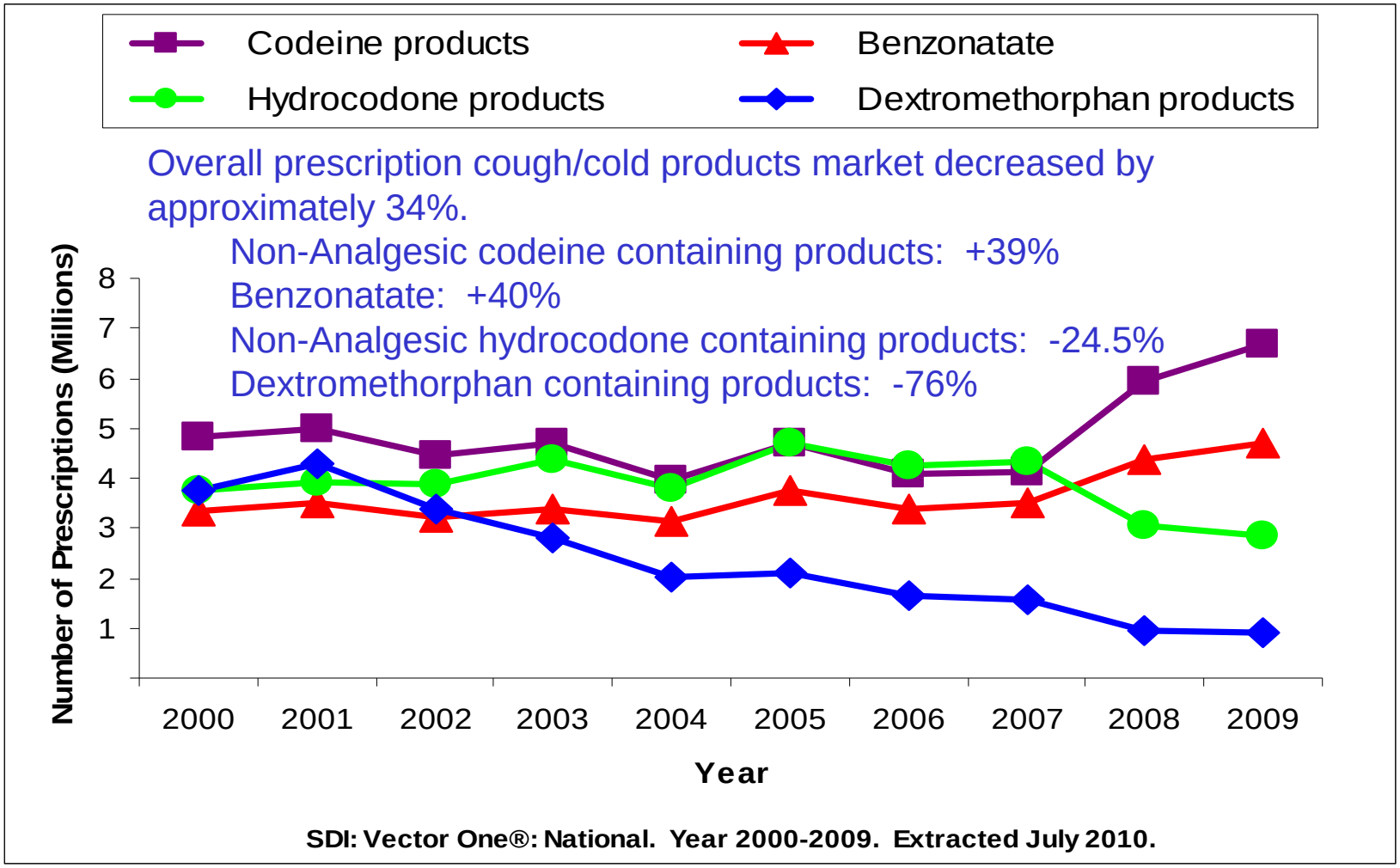
SDI: Vector One®: National. Years 2000-2009. Extracted July 2010.

Prescription-Level Data for Cough/Cold Products

Years 2000-2009

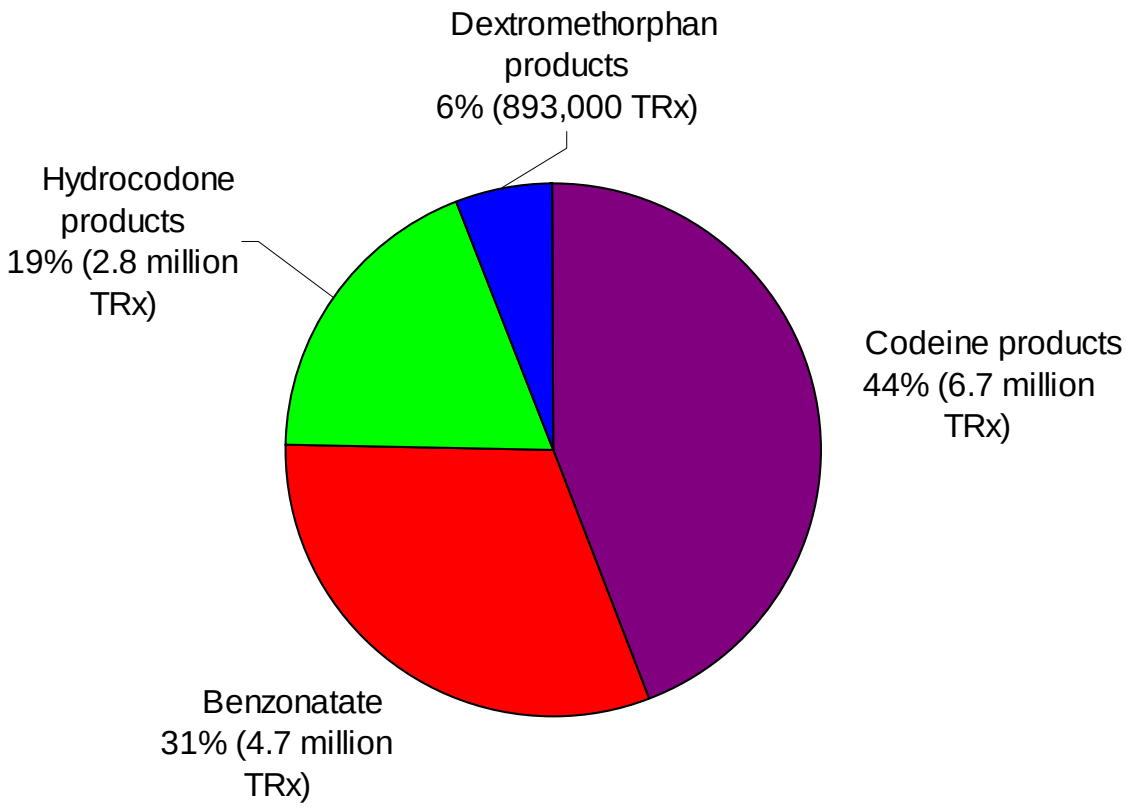
SDI, Vector One®: National (VONA)

Projected Number of Outpatient Dispensed Prescriptions for Cough/Cold Products, Years 2000-2009



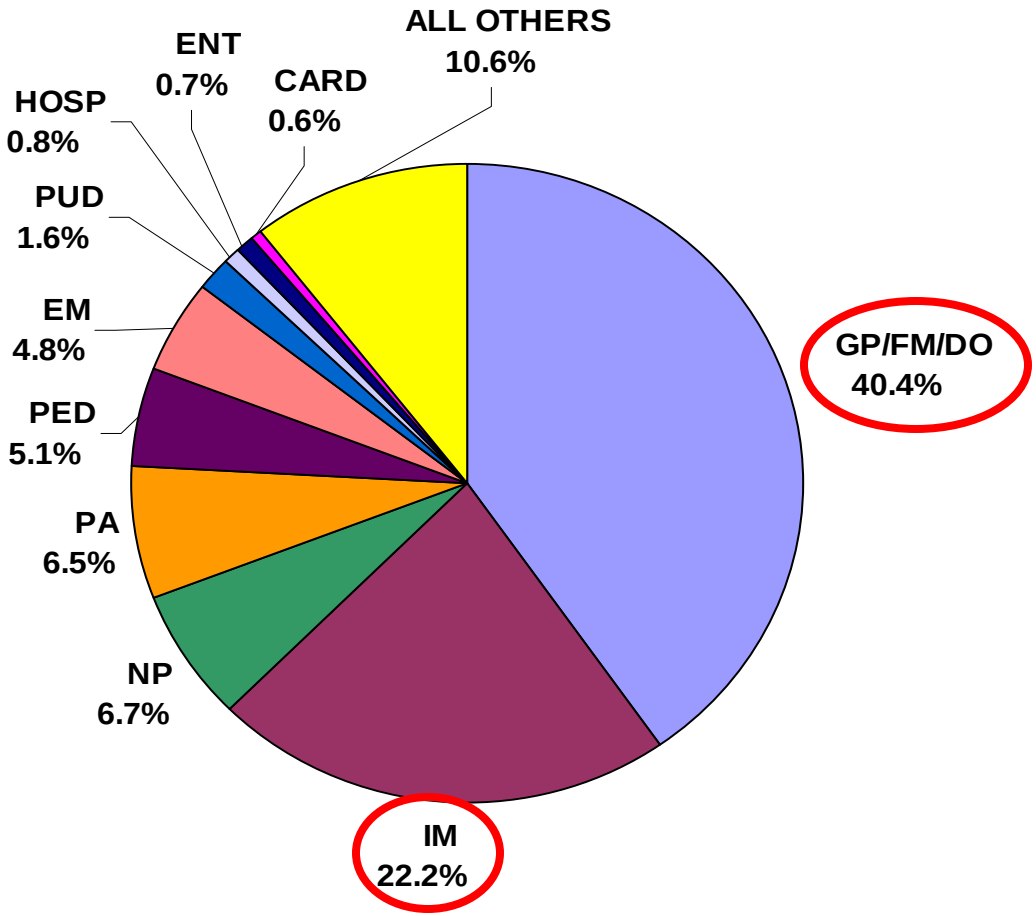
SDI: Vector One®: National. Year 2000-2009. Extracted July 2010.

Market Share Percentage of Outpatient Dispensed Prescriptions for Cough/Cold Products, Year 2009



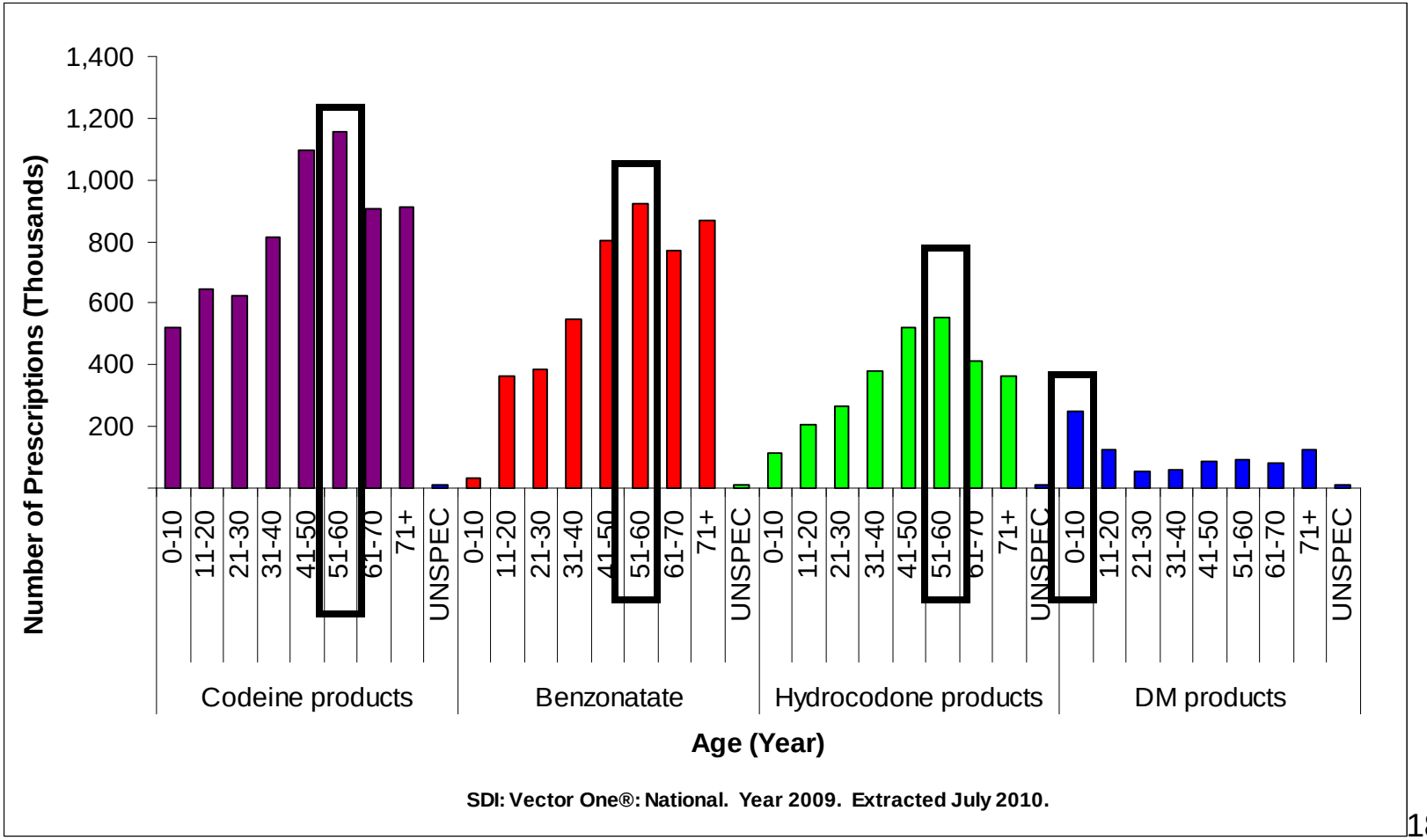
SDI: Vector One®: National. Year 2009. Extracted July 2010.

Top 10 Prescribing Specialties for Cough/Cold Products, Year 2009



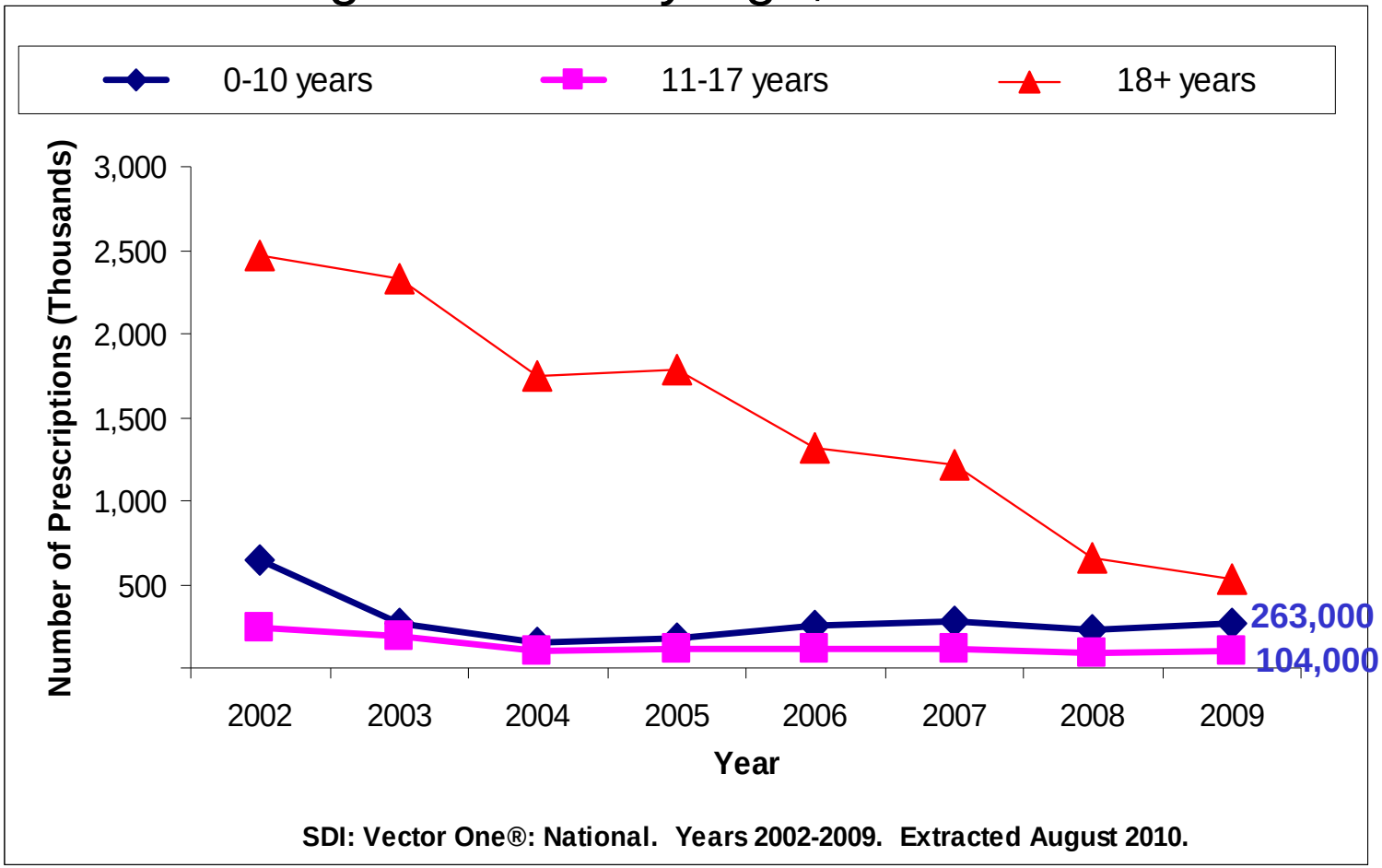
SDI: Vector One®: National. Year 2009. Extracted July 2010.

Total Number of Dispensed Prescriptions for Cough/Cold Products by Age, Year 2009



SDI: Vector One®: National. Year 2009. Extracted July 2010.

Total Number of Dispensed Prescriptions for Dextromethorphan Containing Products by Age, Years 2002-2009



Limitations

- OTC sales analysis
  - Captured approximately 50% of all OTC sales
  - Using sales volume as surrogate for use
    - Unable to determine user demographics
    - Unable to determine frequency or amount of OTC products used at the consumer level
    - Unable to determine concurrent product use
- Dispensed prescription analysis
  - Only describing outpatient prescription use
    - Products captured only as a prescription claim
    - OTC sales not captured

Summary

- Sales of OTC and prescription dextromethorphan products increased during the examined period.
- OTC single-ingredient and combination dextromethorphan products accounted for 6.5% and 90% of overall sales, respectively.
- Prescription dextromethorphan products accounted for 3.5% of overall sales.
  - Prescription dextromethorphan containing products were dispensed less than benzonatate, non-analgesic codeine- and hydrocodone-containing products.
  - General practice/family medicine/osteopathic specialists were the top prescribers.
  - Patient population aged 0 to 10 years old received the majority of dispensed prescriptions for dextromethorphan containing products.

Postmarket Reports for Dextromethorphan and Abuse from FDA's Adverse Event Reporting System (AERS)

Drug Safety and Risk Management Advisory Committee Meeting
September 14, 2010

Sara Camilli, Pharm.D.
Division of Pharmacovigilance II
Office of Surveillance and Epidemiology
FDA Center for Drug Evaluation and Research

Outline

1. Background: AERS
2. Highlight dextromethorphan (DM) and abuse AERS cases presented in the briefing document
3. Provide additional information from a review of AERS abuse cases associated with select brand name products (Coricidin and Delsym)

Background: AERS

- FDA database that captures postmarket adverse event reports
- Reports submitted by healthcare professionals and consumers (voluntary)
- Includes U.S. and foreign reports
- Strengths (potential for large scale surveillance)
- Weaknesses (underreporting, incidence rate, report quality)

DM Cases of Abuse in AERS (2004-2008)

- AERS searched for DM (as active ingredient) cases associated with “abuse” for 5-year time period (2004 thru 2008)
- Includes abuse, misuse, dependence & overdose
- Identified 177 U.S. and foreign cases
  - 33 cases: DM single-ingredient product
  - 17 cases: DM + guaifenesin products
  - 127 excluded because the product contained multiple ingredients or there was insufficient information

DM Cases of Abuse in AERS (2004-2008)

Product	DM Only	DM + Guaifenesin
# of Cases Reviewed	33	17
Median Age in Yrs (range)	20 (2-43)	26 (15-76)
% Male	66	64
Deaths	3	5

DM Cases of Abuse in AERS (2004-2008) Deaths

- DM only deaths (n=3)
  - Male with DM overdose. Drug screen: DM and “illicit” drugs
  - 18 yo male with multiple drug overdose (hx of using DM “regularly”)
  - 22 yo with DM overdose
- DM + guaifenesin deaths (n=5)
  - All associated with intentional suicide

Coricidin and Delsym: Product Descriptions

- Coricidin
  - 5 OTC product combinations with DM
  - 10, 15, or 30 mg DM per tab
  - Co-active ingredients: analgesic (acetaminophen), antihistamine (chlorpheniramine/doxylamine), expectorant (guaifenesin)
- Delsym (dextromethorphan polistirex)
  - Extended release suspension
  - 30 mg DM HBr per 5 mL

Coricidin and Delsym Cases of Abuse in AERS (marketing – 2009)

- AERS searched for U.S. Coricidin or Delsym cases associated with “abuse” (marketing through 2009)
- Includes abuse, misuse, dependence, & overdose
- Excludes pediatric accidental exposures & Coricidin products without DM
- Identified:
  - 246 Coricidin cases
  - 34 Delsym cases

Coricidin and Delsym Cases of Abuse in AERS (marketing – 2009)

Product	Coricidin (n=246)	Delsym (n=34)
Median Age in Yrs (range)	16 (10-31)	30 (14-79)
% Male	63	62
% Associated with Abuse as Reason for Use	98	75
Median QTY Consumed for Abuse (range)	16 tablets (3-64)	300 mL (150-600)

Coricidin and Delsym Cases of Abuse in AERS (marketing – 2009)

Product	Coricidin (n=246)	Delsym (n=34)
Most Frequently Reported Product	HBP Cold & Cough	---
Outcomes:		
# Hospitalizations (includes ER Visits)	129	16
# Deaths	8	4

Coricidin and Delsym Cases of Abuse in AERS (marketing – 2009): Deaths

- Coricidin (n=8)
  - 20 yo male suicide (Coricidin + “other drugs”)
  - 15 yo female OD (Coricidin + alcohol + morphine)
  - Others: gun shot wound (3 cases), car accident, cocaine/heroin OD
- Delsym (n=4)
  - 42 yo male taking Delsym (recommended dose) + thioridazine
  - 63 yo male abuse (Delsym + acetaminophen + alcohol)
  - 32 yo male accidental OD (Delsym + “other drugs”)
  - Other: suicide after Delsym abuse

Conclusion

- AERS review suggests that the use of DM has been associated with intentional misuse of products for abuse purposes.

Findings from the Drug Abuse Warning Network (DAWN):

An analysis of single ingredient Dextromethorphan Containing Products

Catherine Dormitzer, PhD, MPH
Division of Epidemiology
Office of Surveillance and Epidemiology

Outline

- Background
- Methods
- Findings
- Summary
- Conclusions

Drug Abuse Warning Network (DAWN)

- Administered by the Substance Abuse and Mental Health Services Administration (SAMHSA)
- Stratified probability sample of hospitals
  - Short-term, general, non Federal hospitals with 24-hour emergency departments (EDs)
- National estimates account for:
  - Sample design
  - Hospital non-response
  - Partial non-response in responding hospital

DAWN: Selection of Comparator Drugs

- Single ingredient products
- Comparator Products
  - Diphenhydramine
  - Pseudoephedrine
  - Codeine C-V Respiratory agents

DAWN: Case Types

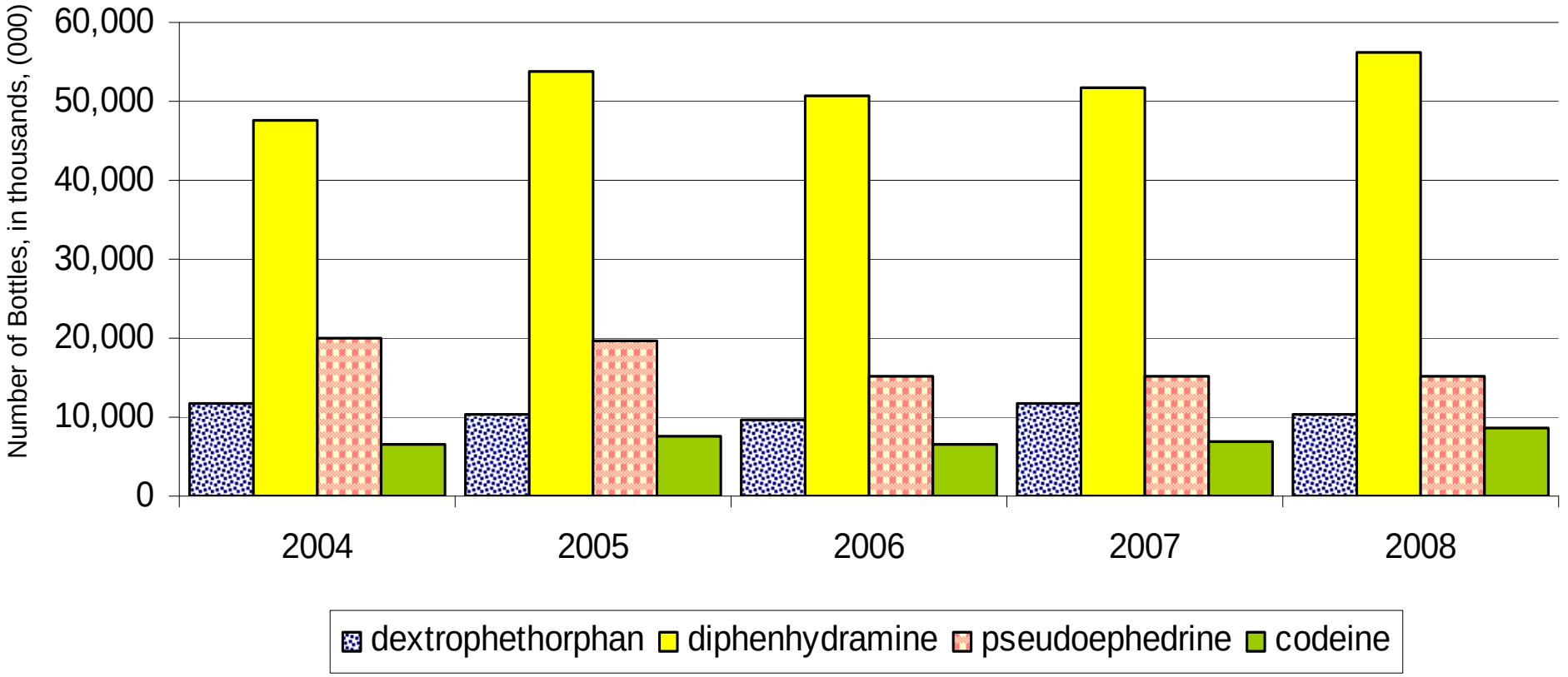
- Case Type
  - Suicide Attempt
  - Seeking Detox
  - Adverse Reaction
  - **Overmedication**
  - **Malicious Poisoning**
  - Accidental Ingestion
  - **Other/Abuse Related**
- All Misuse and Abuse ED Visits (ALLMA)
  - includes overmedication, malicious poisoning, “other” and cases where illegal drugs or alcohol were present

DAWN Analysis

- **Proportion of All ED Visits related to Misuse and Abuse (ALLMA)**
- **Number of ALLMA ED Visits per 100,000 population**
  - 12-17 years of age
  - 18+ years of age
- **Abuse Ratio:**

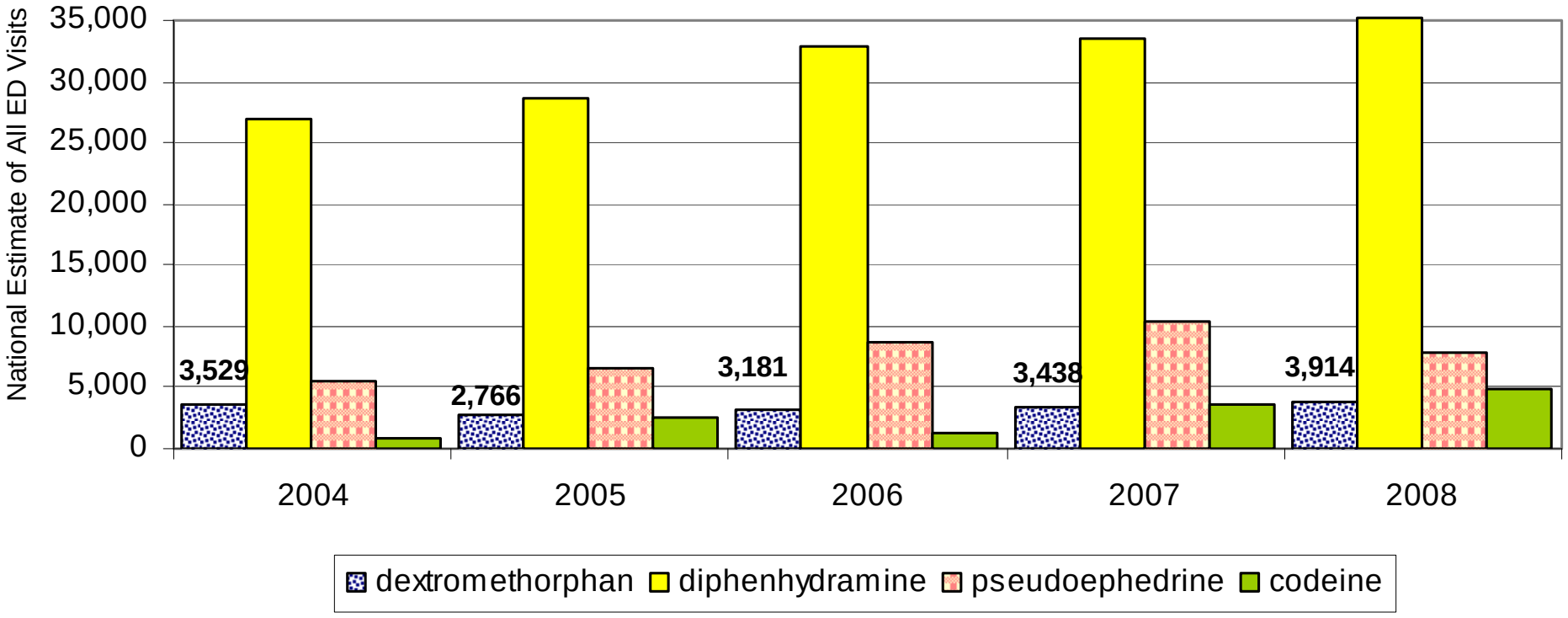
$$\frac{\text{national estimates of ALLMA ED visits}}{\text{10,000 bottles}}$$

Sales of Over-the-Counter and Prescription Dextromethorphan and Comparator Products, 2004-2008



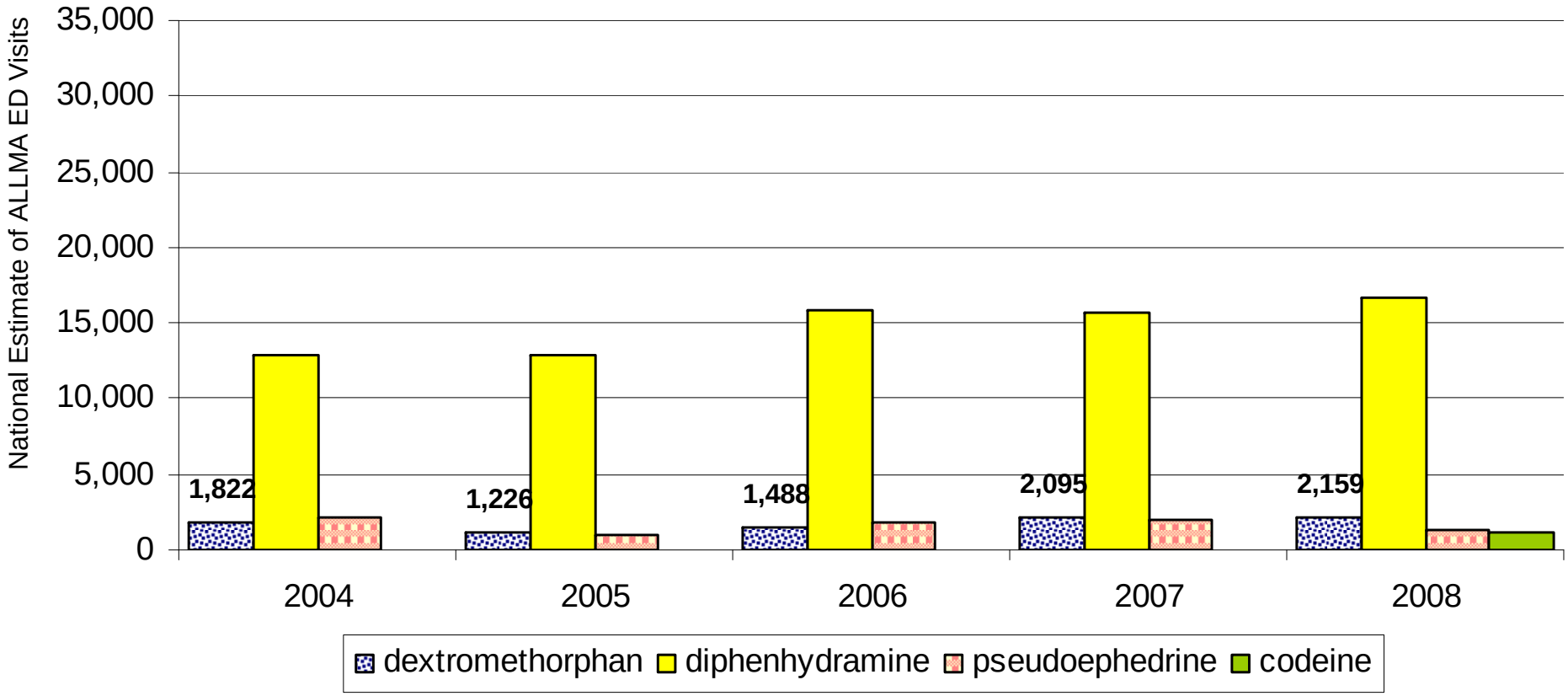
Source: IMS Health, IMS National Sales Perspectives™, Years 2004 - 2008, Extracted 11-4-09, and 3/8/10

DAWN: National Estimates of All ED Visits by Year and Drug Type, 2004 - 2008



Source: DAWN 2004-2008, SAMHSA

DAWN: National Estimates of *ALLMA* Related ED Visits by Year and Drug Type, 2004-2008



Source: DAWN 2004-2008, SAMHSA

DAWN: Proportion per Drug of ED Visits Associated with Drug Abuse (ALLMA), 2004 -2008

	2004 (%)	2005 (%)	2006 (%)	2007 (%)	2008 (%)
Dextromethorphan	52	44	47	61	55
Diphenhydramine	48	45	48	47	47
Pseudoephedrine	39	16	21	19	17
Codeine	…	…	…	…	22

Source: DAWN 2004-2008, SAMHSA

DAWN: Number of ALLMA ED Visits per 100,000 Population by Age Group: 2004 – 2008

Number per 100,000 population: 12-17 years of age					
Year	**2004**	**2005**	**2006**	**2007**	**2008**
ALLMA ED Visits	...	2.3	...	...	1.9
Number per 100,000 population: 18+ years of age					
Year	**2004**	**2005**	**2006**	**2007**	**2008**
ALLMA ED Visits	0.3	0.2	0.4	0.5	0.6

Source: DAWN 2004-2008, SAMHSA

Abuse Ratio: Number of ALLMA ED Visits per 10,000 Bottles 2004 – 2008

	2004	2005	2006	2007	2008
Dextromethorphan	1.5	1.2	1.5	1.8	2.1
Diphenhydramine	2.7	2.4	3.1	3.0	3.0
Pseudoephedrine	1.1	0.5	1.2	1.3	0.9
Codeine	...	...	...	...	1.3

*Source: SDI Vector One®: National (VONA). Extracted June, 2010

Summary

- The number of abuse related ED visits per 100,000 population was higher in the younger age group.
- Overall, the proportion of ED visits associated with misuse and abuse of dextromethorphan was higher than for all the comparator products.
- Abuse ratios for dextromethorphan were higher than those for pseudoephedrine and codeine products, but lower than the abuse ratios for diphenhydramine products.

DAWN -- Limitations

- Only single ingredient dextromethorphan products were included in this analysis.
- Abuse of these products may not result in a medical event that requires an emergency room visit.
- Fatalities are not captured by DAWN ED data.

Conclusion

- DAWN data suggests that use of dextromethorphan products is associated with intentional misuse and abuse.
- Because of the limitations of this data source, the extent of abuse of dextromethorphan products cannot be determined.